BRAIN

A JOURNAL OF NEUROLOGY

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Brain

A Journal of Neurology

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BRAIN

VOL. 69, PART 1.

THE SOMATIC RECEIVING AREA IN THE BRAIN OF THE SHETLAND PONY.

BY E. D. ADRIAN.

(From the Physiological Laboratory, Cambridge.)

IN a paper describing the afferent areas of the brain in various ungulates (Adrian, 1943) an account was given of the somatic receiving area in the Shetland pony, but a detailed map was only made in one animal and this dealt mainly with the representation of the nostril. Two more ponies have now been examined. The results are in general agreement with those already reported and give further information about the representation of the trunk and limbs. An interesting feature is the great convergence of pathways from the limbs compared with the detailed representation of the nostril.

METHOD.

The method was that used in the earlier investigation and consists in exploring the electrical activity of different regions of the cortex with the aid of an amplifier and loud speaker. Since the ear cannot detect very low frequencies, the potential oscillations developed by the cells of the cortex are scarcely audible, but action potentials in the afferent fibres are easy to recognize, even though in a photographic record they would be completely obscured by the slower and larger cortical waves. For this reason it is not necessary to abolish all spontaneous cortical activity by very deep anæsthesia or to use an electrical filtering system to give prominence to the afferent discharges.

The ponies were anæsthetized with dial and were supported on a wooden bench in the normal standing position with the head resting on sandbags. The skull was exposed and opened and an ebonite block was fastened to it carrying an electrode which could be brought into contact with different regions of the cortex. A spiral of silver wire was sewn to the soft tissues of the head to form an indifferent lead. The cortical electrode was either a tuft of moist cotton-wool or an enamelled silver wire bared at the tip and coated with silver chloride. The amplifier and loud speaker system were so arranged that electrical shielding of the animal was unnecessary.

The electrode was placed in contact with various regions of the exposed brain until a position was found in which a touch on the opposite nostril produced the characteristic sound of a volley of impulses in the afferent fibres of the cortex.

The nostril region was the easiest to identify. Once it had been found the whole somatic receiving area could be explored in detail by moving the electrode to different points on the cortex and finding the corresponding points on the body surface where a touch would give an audible discharge. To investigate the effects in single afferent fibres (or single conducting units) the wire electrode was inserted so that the exposed end was 1·5 to 2 mm. below the surface. A feather or light wooden rod was used to stimulate the hairs and skin surfaces. Corresponding points on the body surface and cortex were marked in on sketches of the brain; reference points were also marked on the brain itself with Indian ink. At the end of the experiment the brain was removed, hardened and photographed.

Results.

For the reasons given in the earlier paper the term "Somatic receiving area" will be used to denote the cortical region to which afferent impulses

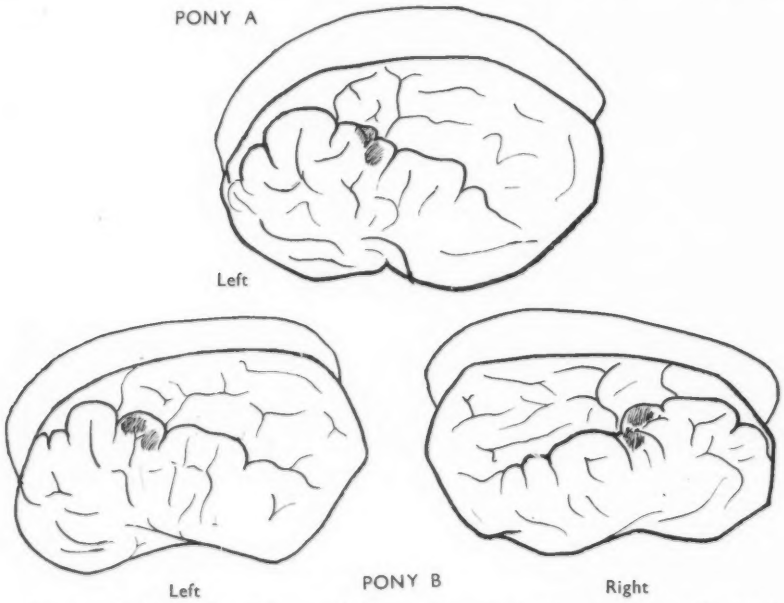

Fig. 1.—Position of somatic receiving area in the brains of the two Shetland ponies, A and B.

are sent when cutaneous receptors are stimulated. This term seems preferable to "Sensory Area" because the latter is often used with some entirely different criterion in mind.

The results for both ponies are in very good agreement. Both were foals 6 months old; one, referred to as Pony A, was a male of 80 kilos and

the other, Pony B, a female of 79 kilos. In Pony B both hemispheres were explored, in Pony A only the left hemisphere.

The horse's brain is highly convoluted but the deep suprasylvian fissure makes a good guide to its topography. In the earlier account the somatic receiving area was said to lie lateral and aboral to the sulcus coronalis in the convolutions of the system of the fissura diagonalis. The same description may be applied to the area found in the present experiments, but the exact position can be better appreciated from the three diagrams in fig. 1 and the photograph in fig. 2.

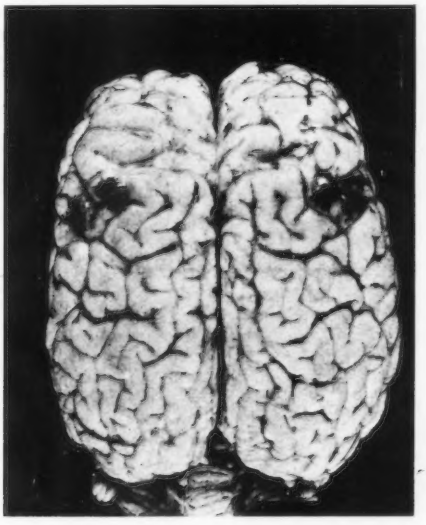

FIG. 2.—Brain of Pony B with receiving areas marked in Indian ink.

The somatic receiving area is divisible into an anterior part concerned entirely with the representation of the opposite nostril and a part posterior and lateral to it concerned with the body and limbs. The nostril region had already been explored in the earlier investigation and a map of it was published (Adrian, 1943, fig. 7). This earlier map agrees very well with the present results and the agreement is the more satisfactory in that the earlier records were not consulted until after the new maps were made. The general arrangement is that the anterior part of the nostril sends discharges to the anterior and lateral part of the cortical area, and the posterior part of the nostril to the posterior and mesial part of the cortical

area. This is illustrated in the two maps in fig. 3, which gives also a redrawing of the older map for comparison. For the middle part of the nostril the agreement is less precise. The differences may be due in part to faulty localization of the stimulus, for it is difficult to be sure that the hair movements are restricted to the region which is touched. The discharges all came from the contralateral nostril. None were detected from the upper or lower lip, but only the exposed surface of the cortex was thoroughly explored and it is possible that the receiving area extends into the cortex on the lateral face of the suprasylvian fissure.

The receiving area for the body and limbs is separated from that for the nostril by a shallow sulcus. On the surface the size of the body

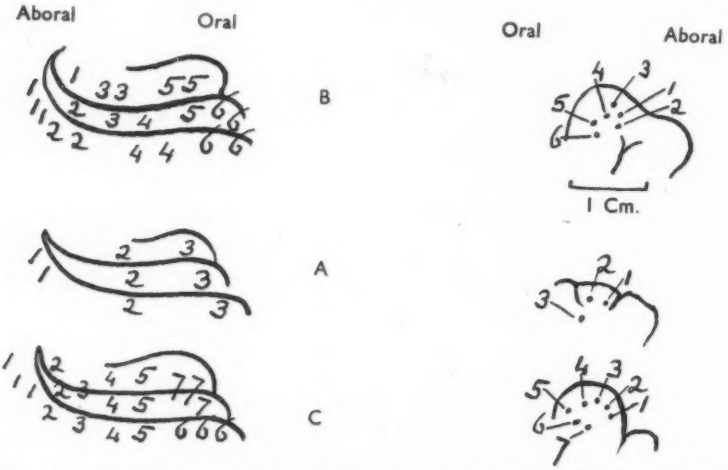

FIG. 3.—Detailed representation of the right nostril in the left hemisphere in Ponies A and B, compared with that found previously (marked C).

and limb area is roughly equal to that of the nostril area, both covering about ·5 cm.² of the exposed cortex. The localization of different regions of the body is shown in fig 4. It has had the same general pattern in all three areas explored (Pony A left hemisphere and Pony B, right and left), the fore-limb sending impulses to the anterolateral, the hind-limb to the posterolateral part of the area and the head, neck and trunk to the mesial part. The more detailed map in fig. 5 illustrates the great convergence of afferent pathways which is the most striking feature of this part of the receiving area. In Pony A, for instance, it was found that touches on the fore-leg at points separated by as much as 30 cm. sent discharges to the

same point on the cortex, whilst at a cortical point only 2 mm. away the discharges were all from the shoulder and back. Here an identical effect seemed to be given by touches at points separated by as much as 40 cm. To elicit discharges from the trunk it was usually necessary to tap the surface lightly; over the fore-leg the movement of a few hairs was enough, and continued discharge could be produced by steady pressure near the knee and pastern.

With the wire electrode thrust into the cortex the afferent impulses

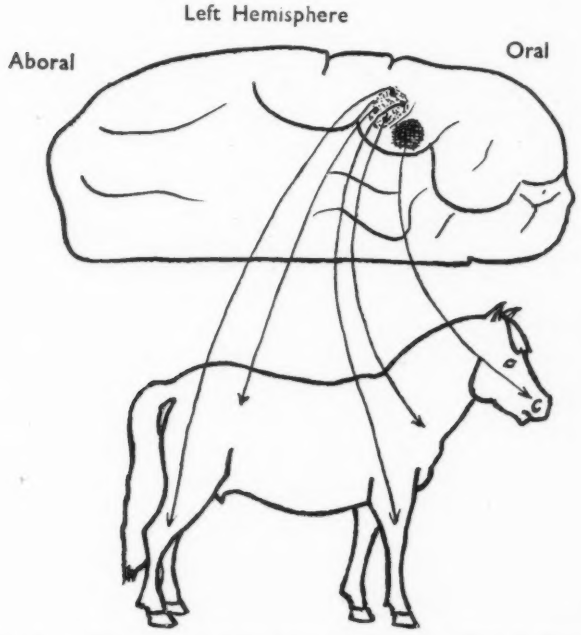

FIG. 4.—Representation of the nostril and body surface in Pony B.

could be heard more clearly but it was difficult to pick up discharges in single units free of interference from others near-by. It is much easier to do this in the cat's brain than in any of the other brains so far examined, and in the ponies only three discharges were found in which the impulses seemed to form a single regular series. Two were produced by pressure on the fore-limb and the other by pressure at the shoulder. One from the fore-limb illustrated the convergence of pathways very clearly for it

could be obtained both by pressure round the pastern or just below the knee 17 cm. away.

All the discharges which were detected, whether by the superficial or the deep electrode, came from the opposite side of the body.

Discussion.

Since the whole surface of the body and limbs on one side has to be represented in a cortical area which on the surface measures only ·5 cm.² in extent, the great convergence of pathways is not surprising. A very rough estimate of the areas involved can be made by treating the body, head and neck and limbs as cylinders. Reckoned in this way half the surface of Pony B works out as 11,000 cm.² Thus the ratio of body surface to cortical receiving area is as 22,000 to 1. For the nostril on the other hand the

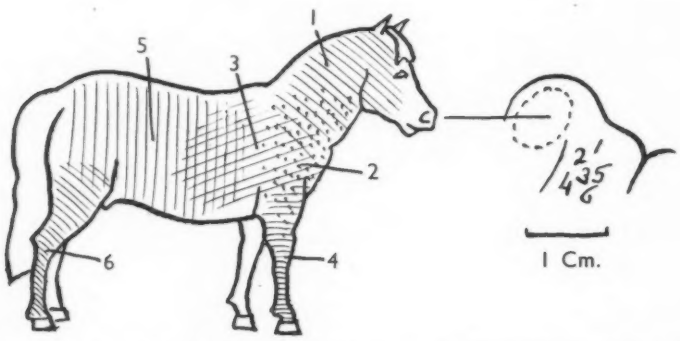

Fig. 5.—Skin areas sending afferent discharges to different points in the receiving area (Pony B).

cortical area on the surface of the brain is again ·5 cm.² but the receptive field connected with it covers only 14 cm.² The ratio of receptive surface to cortical receiving area is therefore as 28 to 1. This again is a very rough estimate, but it is of the same order as the ratio of receptive surface to cortical area in the case of the pig's snout (10 to 1) and the human hand (75 to 1) (Adrian, 1943).

Although the failure to detect afferent discharges from the lips does not prove the complete absence of any representation of the lips in the cortex, it is none the less probable that the pathways from the nostrils are much more extensive. This is sufficiently explained by the use which the horse makes of the hairy nostrils for exploration. In feeding it is the nostril region which is brought into contact with the fresh grass in front

of the head. The hairless lips do not play an important part in selecting food and the nerves supplying them are much smaller than those to the nostrils.

The nostril region in the pony, with its detailed representation in the opposite cerebral hemisphere, recalls the snout region in the pig. The localization of different points in the receiving area follows the same pattern. in that the parts nearer the mouth lead to the anterior part of the receiving area. But the arrangement in both horse and pig is in sharp contrast to that in the sheep and goat where the main afferent supply to the cortex comes from the upper and lower lip on the same side of the body. It has been suggested that the representation of the lips in the sheep and goat is ipsilateral because in their feeding these animals are guided by smell rather than by sight. It might be argued that the position of the eyes in the head gives the horse a better chance of seeing what he is about to eat, but the feeding habits of the horse and goat are scarcely divergent enough to make the argument convincing. Possibly the explanation may depend on the existence of two different varieties of receiving area, one contralateral and one ipsilateral as well, as reported recently by Woolsey and Wang (1945). The conditions of the present experiments may have been unfavourable for the discovery of small ipsilateral receiving areas. On the other hand the ipsilateral lip area in the goat seems to occupy much the same position in the cortex as the contralateral nostril area in the pony. The explanation must wait, therefore, until other animals have been examined. The cow would be the obvious choice if it were not so inconveniently large.

Summary.

(1) The area of the cerebrum receiving afferent discharges from peripheral receptors has been mapped out by the electrical method in two Shetland ponies. The results agree with those already reported, but give additional information about the representation of the body and limbs.

(2) The receiving area is made up of an anterior part in which the contralateral nostril is represented in considerable detail, and a posterolateral part of about the same size for the contralateral half of the body and the fore and hind limb.

(3) The detailed localization in the nostril area agrees with that already described. In the body and limb area the limbs supply the lateral, and the head, neck and trunk the mesial parts.

(4) Owing to the small area of cortex on which the whole body surface is projected there is a great convergence of afferent pathways. Pressure

receptors separated by as much as 17 cm. have produced discharges in the same afferent unit to the cortex and tactile receptors on the trunk 40 cm. apart lead to identical points on the cortical surface.

(5) Comparison of the ratio of sensory surface to cortical receiving area suggests that the tactile discrimination of the pony's nostril region is comparable to that of the human hand and not much inferior to that of the pig's snout.

(6) No discharges to the cortex were obtained from the lips. Thus the arrangement in the pony, with detailed representation of the contralateral nostril, contrasts with that in the goat and sheep where the main afferent supply to the cortex is from the lips on the same side.

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THE CLINICAL SIGNS OF MENINGEAL IRRITATION.[1]

BY JOHN E. A. O'CONNELL.

ALTHOUGH inflammation of the meninges is a condition which may be assumed to have afflicted man since the beginning of history, the recognition of meningitis as such is a relatively very recent achievement. In ancient times when the classification of disease was largely symptomatological, cases of meningitis were no doubt grouped together with cases of other diseases causing similar striking symptoms such as delirium or coma. According to Kinnier Wilson (1940) cerebral and meningeal inflammation were recognized by Willis and Morgagni in the seventeenth and eighteenth centuries respectively. Then in the nineteenth century certain frequently recurring and widespread types of meningeal inflammation began to be differentiated—in particular tuberculous meningitis and cerebrospinal fever—and it is noteworthy that this differentiation was made at a time when the causative micro-organisms had not yet been discovered. The rapid advances in bacteriological knowledge beginning in the latter decades of the nineteenth century and the introduction of lumbar puncture by Quincke in 1893 placed the recognition of meningitis upon a sound clinico-pathological basis and a new diagnostic era was entered upon. As a result the interest of physicians was stimulated and the clinical features of inflammation of the meninges received more attention. Now, almost fifty years after Quincke's contribution, the introduction of chemotherapy has opened up a new therapeutic era in meningitis and the interest of clinicians has again been stimulated by the improved prognosis in what had in the past proved all too frequently to be a fatal illness.

As in the diagnosis of other infections so in meningitis two groups of phenomena must be considered. In the first place there will be the general features of an infective process—features which will be more pronounced if the infection be an acute one. Secondly and developing later in many cases there will be the evidence of involvement of the nervous tissue and meninges. While such disturbances of consciousness as coma or delirium naturally raise to mind the possibility of an inflammation of the brain it

[1] *A Paper read at a meeting of the Society of British Neurological Surgeons, February,* 1946.

must be remembered that these same symptoms may be of purely toxæmic origin. In themselves therefore they do not permit of the diagnostic localization of the microbic infective process in the central nervous system. The signs which follow inflammation of the meninges will usually form a much sounder basis for such a localization. It is the purpose of this paper to consider these signs of meningitis, but before doing so it should be emphasized that the signs are those of meningeal irritation and may result not only from the presence of inflammatory exudate but also from the presence of blood in the cerebrospinal fluid and perhaps even from other chemical alteration in the fluid. The more important clinical signs of meningeal irritation will now be considered in turn and the various explanations which have been suggested for each of them in the literature will be noted. A series of anatomical observations on the displacements of the spinal cord, spinal nerve-roots and spinal theca which follow movements of the head and lower limbs will then be described. Finally a hypothesis, which is based on these observations, will be put forward to explain the signs of meningeal inflammation.

The Clinical Signs of Meningitis and the Accepted View of the Mechanism Responsible for Them.

Cervical rigidity is probably the most widely recognized and frequently encountered sign of meningeal irritation and indeed the diagnosis of meningitis is rarely made in its absence. It is noteworthy that the rigidity affects in particular the extensor musculature of the neck so that while flexion of the neck may be impossible hyperextension is readily carried out. When this rigidity of the extensor musculature of the neck is well marked there may develop in association with it a second sign of meningitis—head retraction. Kinnier Wilson explains the occurrence of these two signs as being due to the widespread muscular rigidity which may be present in meningitis. Jelliffe and White (1935) class these and other meningeal signs under the heading of motor irritation and include the occasionally occurring epilepsy under the same heading. Grinker (1943) states that cervical rigidity and head retraction occur in conditions in which blood or pus distends the basal meninges and remarks that it is of obscure origin. He adds that perhaps a reflex from inflamed parts diminishes pain. Russell Brain (1940) states that flexion of the neck raises the pressure in the cisterna magna and that when the meninges are inflamed this is painful. Reflex muscle spasm prevents the occasion of this pain.

A third sign of meningitis and one which develops frequently and early in the disease is that of Kernig. When the hip is flexed to a right angle or beyond this full extension of the knee becomes impossible, and not painful only. Kernig described this sign in 1884 pointing out that it had been present in 84 per cent. of his cases of meningitis, and that it was less common in children especially the very young. In a paper written in 1907 Kernig remarks that very little is known about the mechanism by which the sign is produced and he discusses the various explanations which had been suggested for it. Bell had thought that in the presence of cerebral disease extension of the knee with the thigh flexed produced a sustained reflex contraction in the hamstrings. Netter had suggested that the irritability of the spinal roots was increased as a result of inflammation of the meninges. Further he considered that the lengthening of the lumbar and sacral roots caused by hip flexion still further increased their irritability. As long as the hip is extended extension of the knee does not excite a reflex contraction in the hamstrings but when it is flexed such a contraction does occur. Kernig, however, favoured the explanation of Roglet who believed that muscular hypertonia in meningitis is produced by increased pressure and direct irritation of the spinal cord and cauda equina. This hypertonia when it affects the hamstrings, which in a normal individual are barely long enough to permit full extension of the knee with the hip at a right angle, produces the contracture typical of Kernig's sign. In modern textbooks of neurology opinions differ as to the factors responsible for the occurrence of this sign. Kinnier Wilson again states that it is a part of a widespread muscular rigidity. Russell Brain states that in the test the nerve-roots passing into the lower limb are stretched and when the leptomeninges are inflamed and the spinal subarachnoid space is distended this is painful.

A fourth sign is the neck sign described by Brudzinski (1909). When the neck of a patient with meningitis is flexed passively, flexion of the lower limbs occurs at the hips and knees so that the limbs may be strongly flexed on the pelvis. Brudzinski believed that both this sign and his leg sign (which will be next described) occur more frequently than Kernig's sign, though later authors do not agree on this point. Brudzinski points out that the sign is due neither to raised intracranial pressure nor pain, and that it is caused by muscular hypertonia in the lower extremities, and by a physiological preponderance of the extensor muscles of the neck and back over the flexor musculature of the lower extremities. Later both Kinnier Wilson and Wechsler (1943) regard the sign as a tonic neck

reflex. Grinker agrees with the latter view and states that it is quite likely that œdema, pressure, &c., cause a physiological break in the region caudad to the nucleus ruber with the release of lower tonus mechanisms.

Fifthly there is Brudzinski's leg sign—the identical contralateral reflex. When one limb is flexed at the hip and extended at the knee, as in eliciting Kernig's sign, a simultaneous flexion of the opposite limb occurs at the hip and knee. Kinnier Wilson simply states that it is a crossed reflex. Other suggestions as to the basis of this sign have not been encountered.

Finally opisthotonos may be mentioned as an occasional sign of meningitis since in some cases head retraction is but the precursor of this much more severe deformity. In fig. 1 the opisthotonoid posture is vividly represented. This is a photograph of a drawing made by Sir Charles Bell following his observations of three soldiers wounded in the head during

FIG. 1.—Opisthotonos. A photograph of Sir Charles Bell's drawing.

the battle of Corunna. It is widely believed, though not certain, that tetanus was the responsible infection in these cases. However that may be, it is felt that this drawing provides an unequalled demonstration of the posture of the head, trunk and limbs in opisthotonos. Grinker suggests that opisthotonos is an exaggerated posture of decerebrate rigidity and others believe it to be due to the widespread muscular rigidity occurring in meningitis.

These clinical signs of meningitis are widely recognized and readily elicited. Yet it has been seen that at the present time there appears to be little agreement as to the factors responsible for their development, and no causative mechanism common to all of them has been suggested. Indeed a perusal of the literature reveals disagreement as to the mechanism responsible for any one of these meningeal signs. Among the suggested

explanations are widespread muscular rigidity, reflex muscle spasm to prevent painful movements of inflamed parts or painful alterations in intracranial pressure, physiological preponderance of the extensor over the flexor musculature, tonic neck reflexes and crossed reflexes. Some anatomical observations which have seemed to have a bearing on meningeal signs will now be described and upon these will be based a hypothesis which provides a single explanation for the whole group of signs under consideration.

Anatomical Observations.

In early embryonic life the central nervous axis is closely invested by the developing cranium and spinal column so that both the cranial and spinal cavities are largely filled by the brain and spinal cord. Later further enlargement of the skull is accompanied by, and perhaps in part due to, the rapid development of the cerebral hemispheres, and the growth of both continues harmoniously for a considerable period after birth. While growth of the vertebral column continues throughout the latter part of intra-uterine life as well as after birth the growth in length of the spinal cord soon lags behind that of the spinal column. Because of its continuity with the brain-stem at the foramen magnum the spinal medulla undergoes a displacement proximally relative to the spinal canal. The anterior and posterior spinal nerve-roots—especially those arising from the caudal segments of the cord which have undergone the greatest relative displacement—become drawn out as they pass from their points of attachment to the cord to their foramina of exit from the dural theca. While in adult life the dural theca continues to line the greater part of the spinal canal the direction of the extradural nerves in the lumbar spinal canal does suggest that a slight cephalad migration of the dural theca has also taken place within the spinal canal. From the embryological viewpoint one thus gains the impression that a state of mild longitudinal tension will persist in the intraspinal structures—the spinal medulla, its attached nerve-roots and the dural theca.

The effect of movements of the head and lower limbs in producing displacements of and alterations in the state of tension in the intraspinal structures will now be considered. The observations to be described were made in the cadaver, a wide laminectomy being caried out in fresh material. The whole lumbar and dorsal portion of the spinal canal was opened as well as the lower portion of the cervical canal. The extent of the displacement of the dural theca and spinal medulla which follows

movement of the head and neck was then determined as follows: a marker was placed on the surface of the theca or medulla at the level under investigation. This took the form of either a superficial transverse incision or a white thread transversely placed on the theca or medulla. With the head and neck fully extended by an assistant an indicator was placed transversely across the spinal canal at a level exactly corresponding to that of the marker already in position. This indicator consisted of a scalpel blade with its point driven into the cut surface of a vertebral lamina in such a way that the knife edge was perpendicular to the surface of the theca or medulla. The extent of the separation upon full flexion of the head and neck between the fixed (spinal) marker and that free to move with the theca or medulla was then noted in millimetres. This procedure was repeated at various levels in the spinal canal. The extent of the displacement of the theca and spinal medulla which follows movements of the lower limbs was similarly determined. Having placed markers in position with both hips and knees extended the effect of flexing first one and then both hips—the knees remaining extended—was noted. Other observations were made upon the displacement which follows hyperextension of the hip with full flexion of the knee. It has been found, by means of these observations, that the displacements of intraspinal structures which follow movements of the head and lower limbs are capable of measurement and a series of such measurements is described below. A change of tension in a nerve cannot be readily measured however. It is none the less possible to perceive such changes when they are sufficient in degree. A sling of thread may be passed beneath the nerve under examination and held in surgical artery forceps. The mobility of the nerve is then gently estimated and, since this varies inversely with the degree of longitudinal tension, alterations in this mobility secondary to movements of the head and lower limbs can be interpreted in terms of tension. At times indeed the change in tension becomes visible when a lax nerve becomes drawn tight following for example flexion of the hip with extension of the knee. The results of a series of these observations will now be described.

When the head is fully flexed on the trunk a cephalad movement of the dural theca and spinal medulla occurs—the tension in the intradural nerve-roots being increased (fig. 2). Following the opposite movement of full extension of the head a caudad movement of the dural theca and spinal medulla takes place and the tension of the intradural nerve-roots diminishes. The extent of this movement of intraspinal structures varies with several circumstances. It certainly differs with the individual and

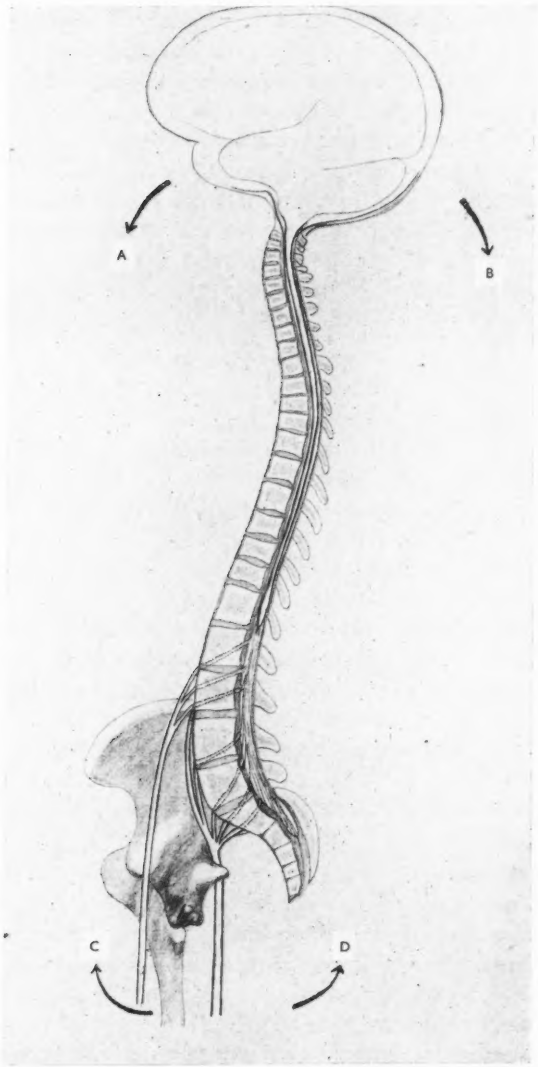


FIG. 2.—Drawing indicating the movements of head and lower limbs which affect intraspinal structures and the effects which they produce.

A. Flexion of head and neck produces cephalad movement of intraspinal structures and increased tension in spinal nerve-roots. B. Extension of head and neck produces caudad movement of intraspinal structures and diminished tension in spinal nerve-roots. C. Hip flexion with knee extended produces caudad displacement of intraspinal structures and increased tension in spinal nerve-roots. D. Hip extension with knee extended produced cephalad displacement of intraspinal structures and diminished tension in spinal nerve-roots.

it is thought likely that it would be greater in young than in old individuals. In four cadavers of which the youngest was 44 years and the oldest 73 years the extent of cord displacement with head movement was found to vary at different levels in the canal. Quoting average figures from this series it was found that the excursion of the cord which followed movement of the head from full flexion to full extension was 5 mm. in the cervical region, 4 mm. in the mid-dorsal region and 1 mm. at the conus. Movement of the dural theca was approximately the same extent and it was noted that full flexion of the head produced a definite increase in tension in the intradural roots and extradural nerves throughout the spinal canal.

Turning to the effect of leg movements in altering the tension in the intraspinal nerves, in a previous investigation (O'Connell, 1943) into the ætiology of certain of the physical signs commonly observed in the presence of lumbar intervertebral disc protrusions it was noted that when one leg was flexed at the hip and extended at the knee the extradural nerves entering the corresponding sciatic nerve were rendered tense. As would be expected a caudad movement of the dural theca follows and there results from the latter a slight increase in tension in the roots of the cauda equina with a caudad movement of the conus. When both hips are flexed simultaneously with the knees extended the extent of the caudad movement of the dural theca is greater than when either is moved alone and, if the spine allowed to flex, may amount to 8 to 10 mm. It has seemed that the greater part of the stretching force which follows hip flexion with knee extension is expended on the dural theca. A smaller but definite increase in tension in the intradural roots does occur, however, and produces a caudad movement of the spinal medulla.

It has been seen that the movement of hip flexion combined with knee extension increases the tension in the intraspinal nerves and roots (fig. 3A). What is the position of the lower limbs in which these structures will be least tense? It is not as might at first be thought the reverse position of hyperextension of the hip with knee flexion. It has been found that such a movement gives rise to an increase in tension in the extradural nerves which enter the femoral nerve (fig 3B), and as with the sciatic nerve-roots this causes a displacement of the dural theca and increased tension in the intradural roots. Thus the posture in which maximum relaxation of intraspinal nerves will occur is one of intermediate degrees of flexion of both hip and knee.

It is believed that these anatomical observations indicate that in certain

postures the normal tension in the intrachecal nerve-roots is increased and that in other postures it is decreased. The anatomical isolation of the spinal medulla is thus less complete than is perhaps frequently imagined.

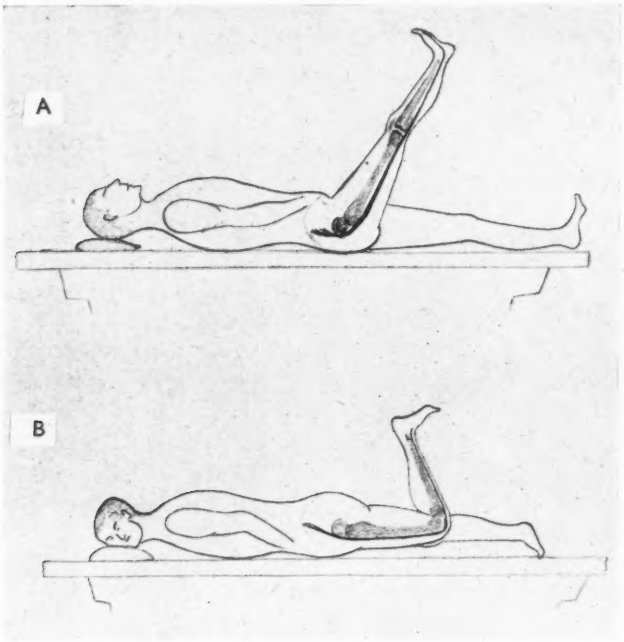


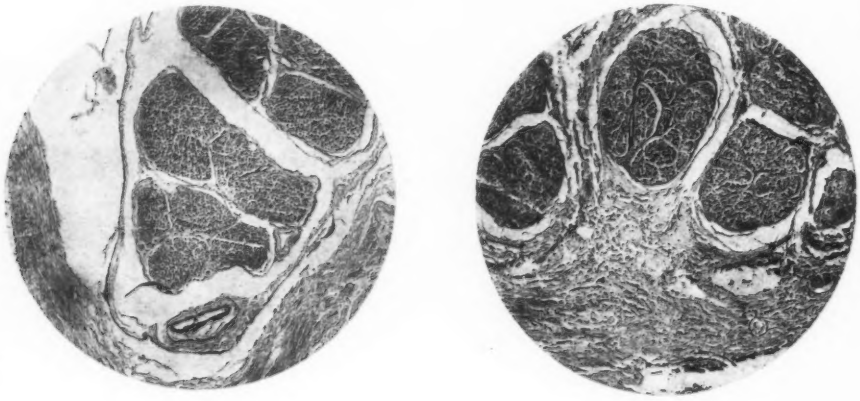
FIG. 3.—A. Drawing to indicate that when hip flexed and knee extended the roots of the sciatic nerve are rendered tense.
B. Drawing to indicate that when the hip is hyperextended and the knee flexed the roots of the femoral nerve are rendered tense.

THE HYPOTHESIS.

It is clear that in meningitis the nerve-roots which are contained within the inflamed leptomeninges will be themselves inflamed. The inflammatory changes in these nerve-roots may be of all degrees of severity and in meningitis of a subacute type may include granulation tissue formation and subsequent fibrosis. In fig. 4 a photomicrograph of a normal intrathecal spinal nerve-root is contrasted with one from a case of meningitis. The latter was obtained at post-mortem from a man who died from a meningeal infection with *Bacillus pyocyaneous* after an

illness lasting five weeks. The great thickening of the arachnoid sheath of the inflamed root is obvious and inflammatory cells can also be observed between the bundles of nerve-fibres. It is likely that the inflammatory changes in the posterior nerve-roots are responsible for the intense posterior cervical and occipital pains which are frequent symptoms of meningitis and like change in other nerve-roots may be responsible for more widespread pains.

It is a justifiable assumption that the spinal nerve-roots as they transverse the inflamed meninges (indeed, as has been shown, roots which are themselves inflamed) will be hypersensitive to mechanical stimulation by compression or stretching. In other acute inflammations such as acute



A B

FIG. 4.—Photomicrographs of transverse sections of intrathecal spinal nerve-roots Mallory's connective tissue stain (× 70).
A. Normal nerve-root.
B. Nerve-root from patient with subacute meningitis.

arthritis and acute peritonitis movements which might occasion painful mechanical stimulation of sensory nerves are prevented by muscle spasm. While the intraspinal nerve-roots are protected from certain forms of stimulation by their anatomical position it has been seen above that they can be subjected to stimulation by stretching produced by certain movements of the head, neck and lower limbs. It is believed that the majority of the signs of meningitis depend upon this fact and that they are due to reflex muscular hypertonia designed to protect the spinal nerve-roots from painful tension stimuli. The signs can be grouped under three

headings: first as postures designed to provide maximum relaxation (minimal tension) in the inflamed nerve-roots; secondly, muscle spasms resisting movements productive of painful tension in these nerve-roots; thirdly, reflex movements designed to relax inflamed nerve-roots when these have been rendered tense by some test manœuvre. Thus cervical rigidity is designed to prevent, in particular, the movement of flexion of the head on the trunk—a movement which it has been seen would stretch the inflamed intrathecal nerve-roots. Head retraction is due to a further increase of protective spasm in the extensor muscles of the neck. In Kernig's sign again the rigidity of the hamstrings is a reflex one designed to prevent the increase in tension in the spinal nerve-roots which occurs when with the hip flexed to a right angle the knee is fully extended. It seems possible that in very young children the extradural nerves passing to the sacral plexus may be more lax than is the case in later years. This has not been confirmed anatomically but it is noteworthy that small children can frequently be seen with the toes of an extended leg in their mouths. Such excessive laxity (if it occur) may explain Kernig's observation that his sign may be absent in the very young.

When the neck is flexed the upward movement of the spinal cord increases the tension in the spinal nerve-roots. A simultaneous movement of flexion of the hips and knees will produce a partial relaxation of the stretched roots—Brudzinski's neck sign may be thus explained. Brudzinski's leg sign (the identical contralateral reflex) may similarly be regarded as a movement which produces relaxation in structures made tense by a test manœuvre—since when flexion occurs at the knee and hip on the side opposite to that of the manipulated limb—a maximum contribution to relaxation of the roots of the cauda equina results. Finally it is possible that this same hypothesis may help in the interpretation of the opisthotonoid posture. On the posterior aspect of the spinal cord within the space of 18 inches all the important afferent fibres from the trunk and limbs gain entry to the cord in linear succession—those of the two sides being separated by less than 1 inch. Each of these roots is exquisitely sensitive to stimulation as shown by operative observations and the extremely characteristic root pain which results when one of them is stretched by the downward movement of an attached tumour before a wave of cerebrospinal fluid produced by coughing or jugular compression. Having gained entry to the spinal medulla it is noteworthy that the sensitivity of the posterior nerve-root fibres to mechanical stimuli is greatly diminished. Again at its peripheral end once a posterior nerve-root has penetrated the dura it is provided with a fibrous tissue sheath and is less

sensitive to stimulation. It seems just possible therefore that the position of opisthotonos in cases of meningitis is a reflex one designed to protect from painful tension stimuli the whole succession of sensory roots in an area in which they are massed close together and peculiarly sensitive to such stimulation. Thus the position of the head, trunk and lower limbs may be explained and it is noteworthy that the adduction and internal rotation of the upper limbs with flexion of the elbows is a position in which the large nerves entering the upper limbs will be rendered lax.

In this hypothesis it has been suggested that the signs of meningitis under discussion are reflex phenomena. The adequate stimulus is one of tension and when it is applied to an inflamed posterior nerve-root muscle spasm is the result. The reflex is thus a protective one. It is interesting to speculate whether or not the hypothesis has any bearing on the occurrence of opisthotonos and other meningeal signs in conditions which it may be assumed that the meninges are not inflamed. Tetanus is the outstanding example of such a condition. It is possible that in the presence of the increased reflex excitability of the spinal medulla in tetanus tension stimulation of normal posterior spinal nerve-roots may be adequate for the production of reflex muscle spasm. Muscle rigidity and postures similar to those much more frequently seen in meningitis might thus be produced. Protection of the posterior spinal nerve-roots in this manner may lead to a diminution of the widespread painful muscular spasm which are initiated by sensory stimuli in cases of tetanus.

Summary.

(1) The chief clinical signs of meningeal irritation have been described and the views which have been held on the mechanism of their production considered.

(2) Anatomical observations have been described upon the effects of movements of the head and lower limbs in producing displacements of intraspinal structures and variations in tension in the spinal nerve-roots. It has been found that such displacements and alterations in tension may be readily observed in the cadaver.

(3) The hypothesis has been put forward that the meningeal signs under discussion depend upon the transmission of tension to inflamed and hypersensitive spinal nerve-roots. The signs are believed to be either postures designed to minimize tension in the inflamed roots, muscle spasms designed to limit movement productive of such tension or movements designed to produce maximum relaxation in nerve-roots rendered tense by some test manœuvre.

In conclusion I must record my debt to those who have assisted in the making of these observations. My assistants at different times have helped with the dissections—in particular Messrs. J. Andrew, C. Hartley and J. Seymour, and I am further indebted to the latter for the three drawings. Dr. A. G. Stansfield has kindly prepared the histological material from which the photomicrographs were made.

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THE DEVELOPMENT OF THE SUBSTANTIA NIGRA.

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Of the structures involved in Parkinson's disease, least is known about the development of the substantia nigra. In his "Manual of Embryology" Frazer confesses that "details of the origin of the substantia nigra are not known," and also that "the actual mode of formation of the red nucleus is quite unknown" (1940). With this paucity of information it seemed desirable to investigate the origin of these two structures before attempting the study of pathological changes in this syndrome (*see* Hassler 1937-8).

In the 8·5 mm. (4½ weeks) embryo the basal lamina of the mesencephalon has developed to a greater extent than the alar lamina. This is due to proliferation of ependymal and peri-ependymal cells, and already the mantle layer of the basal plate exhibits an inner zone of congestion and an outer zone of spread which merges into the marginal zone.

At the 10 mm. stage (5 weeks) polar neuroblasts are visible in the mantle layer, and minute glial cells are recognizable in the marginal layer. The somatic efferent columns have differentiated on either side within the mantle layer. In transverse sections at this stage a characteristic area of proliferation appears in the mid-ventral region of the basal plate between the two somatic efferent columns (fig. 1). This is named the mid-ventral proliferation, and the neuroblasts spread ventrally almost to the surface, and ventrolaterally where they form a lateral angle which penetrates between the somatic efferent column and the marginal zone (fig. 1). [1] From this mid-ventral proliferation and spread it has been found that the red nucleus and the median oculomotor nucleus of Perlia arise (*see* following papers).

At 13 mm. (5½ weeks) the posterior longitudinal bundle can be identified. It occupies a position in the basal plate ventral to the somatic efferent column (oculomotor and trochlear nuclei), and, in consequence, this nuclear column is shifted dorsally. The lateral angle of the mid-ventral proliferation now projects between the posterior longitudinal bundle and the marginal zone (fig. 2). In the 14 mm. embryo the mid-ventral proliferation is well formed, and it causes the approximation of the ventral lips of the cavity, so that the latter is reduced in size and the oculomotor nuclei are brought nearer to the mid-line.

[1] The figures belonging to this Paper are common to it and to the following Paper on the Red nucleus and corpus striatum, and are to be found in the body of that Paper (Plates I to VI).

Series of 13, 14 and 16 mm. embryos all exhibit a corresponding mid-ventral proliferation and spread of cells in the pontine and medullary regions of the hind-brain.

Transverse fibres (brachia conjunctiva) have invaded the mid-ventral proliferation in the mid-brain of a 19 mm. embryo (6½ weeks). In so doing, some of the lateral cells of the proliferation appear to have been displaced still more laterally, where they establish the red nucleus. The ventrolateral angle of the proliferation therefore has the red nucleus, the posterior longitudinal bundle and the oculomotor nucleus lying dorsal to it. In this way the tegmentum of the mid-brain is formed (fig. 3). Each ventrolateral angle approaches the ventral surface.

By the seventh week (22 mm.) the spread of cells from the ventrolateral angle of the mid-ventral proliferation has reached the surface where a thin crescentic stratum is formed. Coincident with the formation of this crescent is the appearance of a narrow band of fibres on its superficial aspect (fig. 4). In longitudinal sections of embryos at this stage, these fibres can be traced from the cerebral vesicle, through the internal capsule and along the basal part of the mid-brain, pons and medulla. They map out the descending cerebral pathway and may be regarded as cerebro-mesencephalic, cerebro-pontine and cerebro-bulbar fibres respectively.

Thus it is evident that the new crescent of cells and the descending cerebral fibres are intimately related. Together they constitute the peduncle. From the crescent the substantia nigra is developed. It is believed that the cells migrate from the ventrolateral portion of the mid-ventral proliferation towards the descending fibres. This affords support for the concept of neurobiotaxis.

By the seventh week of gestation, therefore, three nuclear columns are established in the ventral portion of the mid-brain, the somatic-efferent column, the red nucleus and the substantia nigra. It is significant that each is orientated from the outset in relation to an important fibre pathway, the posterior longitudinal bundle, the brachia conjunctiva and the descending cerebral fibres respectively.

In the pons and medulla, cells from the mid-ventral proliferation are likewise ranged against the descending cerebral fibres. Subsequently the nuclei pontis and the bulbar olive arise from these cells. Thus the substantia nigra, the nuclei pontis and the bulbar olive appear to originate in series from the mid-ventral proliferation, possibly for a similar purpose, to "tap" the descending cerebral stream, and relay cerebral influence into the mid-brain, the pons (and hence the cerebellum) and the medulla.

The crescent of cells recognized as the substantia nigra does not long

persist as such. In the lower part of the mid-brain in 30 mm. embryos it is separated into groups by the descending cerebral fibres which diverge as they enter the pons. In this position the nigral cells effect continuity with the pontine cells (nuclei pontis) and at this early stage the two series are identical histologically. Winkler and Potter (1918-21) in their investigation of the substantia nigra in the cat, observed the continuity between the nigral cells and the pontine grey matter. Shaner (1932), however, found that the cells of the substantia nigra are distinct from those of the pons at all stages of development in the pig.

By the ninth week of gestation (4·0 cm.) grouping of cells occurs in the three nuclear masses in the mid-brain, namely the oculomotor nucleus, the red nucleus and the substantia nigra. At this period the nigral cells are beginning to assume the characteristics of neurones, although they are smaller than those in the oculomotor nucleus.

At the eleventh week (6·0 cm.) the architecture of the substantia nigra is more elaborate. In transverse sections of the mid-brain it is seen to be disposed in two strata, a deeper one occupying the position of the original crescent, and a superficial one embedded among the cerebral fibres. The deeper stratum will be designated the corpus, and the superficial one the cauda. Grouping of cells is evident in the corpus. Well-defined medial and lateral groups are recognized at the respective extremities of the corpus. Between these two groups are three small ones. The cauda begins at the lateral group and arches ventromedially parallel to the corpus, but separated from it by cerebral fibres. It fades away near the medial group (fig. 5).

This reorganization of the substantia nigra seems to be brought about by descending cerebral fibres, which enter the nigral mass separating it into strata and groups. In so doing the fibres themselves are demarcated into two zones, a superficial one covering the ventral edge of the peduncle, and a deeper one lying between the two nigral strata. No cerebral fibres can be traced beyond the substantia nigra into the tegmentum.

Thus it is clear that the descending cerebral fibres are effecting an intimate relationship with the substantia nigra. On following these fibres caudally it is found that the superficial ones descend continuously beyond the mid-brain, while the deeper ones seem to become entangled among the nigral strata. It is not implied that all the deep fibres terminate in the nigra, but possibly at this early stage many of them do arborize around nigral cells, and can be regarded as cerebro-nigral fibres. At the lower levels of the mid-brain the cauda is no longer present, but several small groups of cells are visible among the cerebral fibres. Frequently a blood

vessel is present in the centre of the nigral groups. The nigral neurones at this period are still small and spindle-shaped, their processes being soon lost in the reticulum formed by cerebral fibres and processes of neuroglial cells.

Owing to the stratification of the substantia nigra and the zoning of the cerebral fibres, the peduncles of the mid-brain are better defined, and an interpeduncular space admits blood vessels from the enveloping pial tissue (fig. 6).

During the thirteenth and fourteenth weeks (78 to 90 mm.) the substantia nigra still consists of corpus and cauda. Grouping of its neurones is noticeable in sections, especially the medial and lateral groups of the corpus. These groups belong of course to corresponding columns. Fibre links extend between the corpus and the cauda, and from the cells in the latter, processes are directed ventrally into the cerebral pathway, thus enhancing the intimate relationship already established between the two structures. Between the nigral strata is a dense fibre reticulum enveloping the cells. This is revealed by specific techniques to contain arborizations of cerebral fibres around the nigral neurones.

Shaner (1932) described the development of the substantia nigra in the pig. He found that it appeared in a 50 mm. embryo between the cortical projection tract and the medial fillet. The initial small groups increased to a large loosely collected nucleus in an 80 mm. embryo. In this cell mass the author later identified a lateral group of large cells and a medial group of smaller ones. Shaner quotes Sano (1932) who describes the lateral part of the substantia nigra as the zona reticulata owing to the predominance of fibres within it, and the medial portion as the zona compacta, since in the human adult it retains its earlier composition.

Serial sections at this stage (9·0 cm., 14 weeks) show that the substantia nigra is pyramidal-shaped. Its apex lies in the subthalamic region on the ventrolateral aspect of the subthalamic nucleus. Its base is in the mid-brain-pontine junction. The rostral apex continues into the intermediate portion of the corpus. This is soon flanked by the medial and lateral columns of the corpus which extend to the pons. The separation of the corpus into groups appears to be effected by the cerebral fibres, but, proximally, the passage of the oculomotor fibres to their superficial origin may assist. The cauda is appended to the ventral aspect of the corpus. Small multipolar neurones are present in the substantia nigra.

The descending cerebral fibres are orientated into three systems by the two strata (corpus and cauda) of the substantia nigra. First are the

superficial fibres which are coarse and appear to descend without interruption along the ventral aspect of the mid-brain and beyond. The second system consists of finer fibres which leave the superficial stream and penetrate through the nigra and separate corpus and cauda. These fibres are intersected by, and intermingle with, fibre strands derived from the nigral cells. Thirdly is a fine reticulum of fibrils around the nigral neurones shown by appropriate methods to consist of arborizations of what may be termed cerebro-nigral fibres.

At mid-term the substantia nigra exhibits further development. In addition to the corpus and cauda a new stratum is defined. It will be referred to as the caput. As seen in transverse sections it forms a narrow band of neurones lying between the medial and lateral groups of the corpus along the line of junction between the basis pedunculi and the tegmentum (fig. 7). The tendency to grouping is not obvious in the caput, but outlying (accessory or aberrant) groups of nigral cells extend from it. In sections these are seen to project their processes in strands into the tegmentum on the ventral and lateral aspects of the red nucleus (fig. 7). It is suggested that the caput, by means of these fibre strands, effects connections between the substantia nigra and the tegmentum and perhaps the tectum.

The nigral neurones are by now fairly large multipolar cells. Their coarser processes form fibre bands which link the three strata and penetrate dorsally and ventrally into the tegmentum and crus respectively. Minute dark-brown granules are present in the neurones. As regards size of the mid-brain neurones at mid-term, the largest are the oculomotor cells, the nigral ones are smaller and the rubral cells the smallest.

Apart from general increase in size, no change is visible in the mid-brain during the fifth month (18 cm.). Investigation of the extent of myelination at this period reveals that there are no myelinated fibres in the crus cerebri or within the substantia nigra. Metallic impregnations show that the rostral extremity of the substantia nigra is closely connected by fibres with the subthalamic nucleus.

By the sixth fœtal month, the substantia nigra presents the architecture that is maintained. Its three strata, caput, corpus and cauda, alternate with the two zones of cerebral fibres, deep and superficial. The corpus runs through the deep fibres, the caput completes the peduncle dorsally, and demarcates it from the tegmentum, while the cauda separates deep from superficial fibres. Nigral strands extend between the three strata and project from the cauda into the crus, thus producing the characteristic serrated edge. The close interlocking of the cerebral fibres

and the substantia nigra is seen in fig. 8. Frequently bundles of cerebral fibres are completely enveloped by nigral fibres (fig. 8). From the caput and accessory groups, fibres pass into the tegmentum. These may represent nigro-tegmental or nigro-tectal connections (fig. 7). The superficial zone of cerebral fibres now forms a wide band on the ventral surface of the peduncle.

On tracing the substantia nigra from its rostral to its caudal extremity it is seen that the caput and cauda are present only in the mid-brain. The intermediate part of the corpus commences in the subthalamic region and is very soon divided into five or six columns (or groups when seen in transverse sections) by the cerebral fibres. These columns are flanked by the larger medial and lateral columns throughout the mid-brain. The caudal extremity of the substantia nigra is represented by the medial and lateral columns only, and they extend into the highest part of the pons where their cells are dispersed by the cerebral fibres which fan out on entering the pons.

The usual description of the substantia nigra is that it is disposed in two zones. These were named by Friedeman (1912) the zona compacta and the zona reticulata, his investigation being carried out in primates. Rioch (1929) recognized similar features in the cat and dog, but in addition he identified a pars lateralis lying to the dorsolateral aspect of the main mass. According to Rioch's figures the zona compacta lies medially, just ventral to the red nucleus, while the zona reticulata is more superficial. Interposed between the two zones is a band of fibres, the stratum intermediatum. In Rioch's series (1929) the zona reticulata consists of scattered cells embedded among the fibres of the crus.

Morgan (1927) refers to Malone's findings in the human substantia nigra. Malone described a lateral group of cells as the nucleus intrapeduncularis owing to its being embedded in the lateral part of the peduncle. Previously these cells had been regarded as belonging to the substantia nigra. According to Malone they are "distinctly motor in type, whereas the other cells of the nigra, which are pigmented in man, are distinguished by their structure as sensory in function." Morgan (1927) in his own investigations recognized a lateral elongated nucleus in the cat running along the lateral side of the nigra. Its component cells were different from those of the rest of the nigra, and corresponded to those described in man by Malone as motor and forming the nucleus intrapeduncularis.

Winkler (1918-21) found the substantia nigra to consist of medial, lateral and intermediate columns. Riley (1943) refers to the intermediate part as the neo-nigrum, and the medial and lateral parts as the paleo-

nigrum. The neo-nigrum extends more rostrally into the subthalamus, while the paleo-nigrum reaches the most caudal level in the pons.

In the present investigation, it has been seen that the first nigral stratum to differentiate is the corpus in the 22 mm. embryo (7 weeks). This is soon divided into columns (or groups as seen in transverse sections), of which the medial and lateral ones are first defined and persist as constant entities. The intermediate groups of the corpus are distinguishable later, and increase in number and size as age progresses. Next the cauda is recognizable at 6·0 cm. (11 weeks), and finally the caput with its accessory groups at mid-term. It seems likely, therefore, judging from these observations, that the corpus constitutes the paleo-nigrum, especially the medial and lateral columns. The corpus of the present research, with its medial, lateral and intermediate columns appears to correspond to the zona compacta of Friedeman (1912), while the cauda corresponds to the zona reticulata. No description of the part designated the caput has been found in the literature; but nevertheless it is evident in the fœtal stages (fig. 7).

On the whole the corpus contains larger neurones than the caput or the cauda, but in the latter large ones are present although less obvious, since they are more dispersed and not collected into groups. The caput is certainly made up of smaller cells which are more closely approximated than in the cauda, and not separated into groups as in the corpus. Many large neurones occur in the accessory groups which project from the caput along with fibres towards the tegmentum.

At the eighth fœtal month the Weigert-Pal technique shows that a rich plexus of delicate myelinated processes pervades the substantia nigra. From this plexus, fibres extend to the subthalamic nucleus, the medial lemniscus, the myelinated portions of the crus cerebri, and to the substantia nigra of the opposite side. So far, myelination in the crus has affected all the cerebrospinal fibres, and the deep fibres only of the temporopontine pathway. No fibres in the fronto-pontine tract are as yet medullated.

At full term there is no appreciable alteration in the substantia nigra or peduncle. The dark granules in the nigral neurones are better seen but are still confined to the periphery. In early infancy the accessory nigral groups extending into the tegmentum are very outstanding. Nigral neurones are large and multipolar. Coarse processes can be traced from many of the cells into the crus where they break up and become incorporated among the cerebral fibres (fig. 9). In other cases the processes may be followed for some distance within the substantia nigra where they

terminate in brushlike arborizations against other nigral neurones. It is not presumed that these processes are always the main axon processes.

By the eighth post-natal month, myelination of the fibres in the crus has progressed. The temporo-pontine and cerebrospinal pathways are completely myelinated although the sheaths are as yet delicate; but only the superficial fibres of the fronto-pontine pathway have received myelin sheaths. Thus the deeper fibres of the temporo-pontine tract myelinate before the superficial ones, while the superficial fibres of the fronto-pontine pathway myelinate before the deeper ones. The substantia nigra is pervaded by a dense reticulum of delicate medullated fibres which continues locally into the tegmentum and the crus.

By metallic techniques it is seen that fibres from the crus enter the nigra and arborize around nigral neurones. These are cerebro-nigral fibres. Cajal (1911) believed that collaterals of the motor tracts reached the cells of the substantia nigra. Others including Mingazinni (1889), Kolliker (1896), Bauer (1909), and Foix and Nicolesco (1922) described the entrance of fibres into the substantia nigra from the cerebral peduncle. On the other hand Munzer and Wiener (1902) denied the presence of cortico-nigral fibres. The present research has shown that from early fœtal life fibres do enter the substantia nigra from the descending cerebral pathway. Metallic impregnations also reveal the passage of processes from nigral cells into the crus. Thus an intimate relationship is seen to exist between the descending cerebral pathways and the substantia nigra (fig. 9).

During the second and third years the mid-brain enlarges considerably. The length of the substantia nigra (as estimated in serial sections) is 9 mm. by the end of the second year and 13 mm. at the end of the third year. The architecture of the substantia nigra is maintained, but sometimes the caput, corpus and cauda are not so easily distinguished. This is due to the progressive enlargement of the crus dependent on the intensification of myelination, and the consequent greater separation of the nigral strata and dispersal of the neurones or groups of neurones. Very likely all the nigral neurones are differentiated by birth or early infancy, as is believed to be the case in the brain generally. It is possible that more fibres enter the peduncle and assist in its enlargement.

Between the fourth and fifth years the length of the substantia nigra is 15 mm. It still exhibits its specific arrangement into caput, corpus and cauda. The medial and lateral groups of the corpus are outstanding and constant. Seven or eight groups form the intermediate part of the corpus. The caput and its accessory groups appear to carry nigral connections

towards the tegmentum, while the corpus and cauda are freely intermingled with the crus. The neurones possess brown or black granules, but not all the cells contain them, nor are they present always in the larger ones, many smaller neurones being heavily granulated.

The presence of these brown-black granules is puzzling. They are usually regarded as pigment of the nature of melanin, but as far as can be judged from the literature, this has never been proved. Bloch (1927) formulated a test for melanin based on the reaction of dihydroxyphenylalanine (dopa) upon a substance (dopa-oxidase) which is an intracellular enzyme. He considers the dopa-oxidase to be responsible for the formation of the black substance which he regards as melanin. This is called the dopa-reaction, and techniques are described by Bloch (1927) and Laidlaw (1932) for demonstrating the presence of melanin in the epidermis of the human skin, nævi, melanoblastic tumours and elsewhere. It was considered that the dopa-reaction might be applied to the substantia nigra with advantage, but it was realized from the outset that post-mortem human material would be unsuitable. It is hoped to pursue this problem later.

From this developmental survey it can be stated that:

(1) The nigral cells are identical with neurones in their structure and development, except for the black granular material they acquire.

(2) They arise as unipolar cells and exhibit multipolarity at 9·0 cm. (14 weeks). By the third post-natal year they attain their maximum size.

(3) Brown granules are first seen in the nigral neurones at mid-term (19 cm.). They are minute and scattered here and there at the periphery of the cells. Between mid- and full-term the granules increase, but are still confined to the edges. Not all the nigral cells contain them, nor are they present always in the larger ones. By birth, and subsequently, no difficulty is encountered in finding neurones containing black granules. They often occupy the whole of the cytoplasm or may be confined to one pole, or may even extend into the larger processes.

(4) Myelination of the processes of some of the nigral cells is apparent at the eighth fœtal month.

At puberty the substantia nigra exhibits adult characteristics, although it retains the organization established in fœtal life. The three nigral strata, caput, corpus and cauda, are evident, and in the corpus the medial, lateral and intermediate columns (groups) are distinguishable. Accessory groups from the caput project their fibres into the tegmentum and these can be traced towards the red nucleus, the lemnisci and the posterior longitudinal bundle.

By dissection it is confirmed that the substantia nigra in the adult is a pyramidal mass with its apex in the subthalamus and its base in the proximal region of the pons (fig. 10). Its three sides, dorsal, ventral and medial, are discernible. The whole is immersed in the cerebral fibre pathways, and the penetration of fibres into the nigra can be appreciated.

Evidence of the following connections of the substantia nigra was based first on the observation of fibre strands originating in nigral neurones and traceable therefrom; and secondly on the ability to follow fibres from outside sources into the substantia nigra where arborizations were seen. Specific histological techniques facilitated these observations.

(1) Nigro-peduncular fibres. The penetration of nigral processes among the cerebral fibres in the crus was clearly visible. The "serrations" on the ventral aspect of the substantia nigra contain such fibres. Of course it was not possible to trace the ultimate destination of these fibres, but in many cases nigral fibres were observed to break up into brush-like processes which ramified between and around the peduncular fibres.

(2) Nigro-tegmental fibres. Strands of nigral fibres were seen to extend from the caput, from the accessory groups, and from the medial and lateral groups of the corpus into the tegmentum. Here they were directed towards the red nucleus, the lemnisci and the posterior longitudinal bundle. Nigro-tectal fibres could not be distinguished from the nigro-tegmental ones. Rioch (1929) identified and named the tractus nigro-tegmentalis in carnivora.

(3) Intra-nigral links. Processes from nigral neurones could be followed towards other neurones in the vicinity where they ended in brush-like arborizations.

(4) Inter-nigral links. These were seen to pass from one side to the other deep to the interpeduncular space. It was not possible to find how far these fibres were concerned with the nucleus interpeduncularis or the nucleus tractus peduncularis transversi as described by Rioch (1929).

(5) Subthalamo-nigral intercommunications. These were demonstrated clearly by metallic impregnations and appeared to be very rich. Rioch (1929) and others have described a tractus subthalamo-nigralis (fig. 11).

(6) Cerebro-nigral fibres. Entrance into the substantia nigra of fibres from the crus cerebri were seen from early fœtal life. As already stated, Foix and Nicolesco (1922), Cajal (1911), and others described cortico-nigral fibres, but Munzer and Wiener (1902) denied the presence of such fibres.

(7) Optico-nigral links. In several specimens fibres were observed to leave the optic tract and to take a trans-peduncular route into the substantia nigra. In all cases the connection was with the lateral or medial group of the corpus (paleo-nigrum). This connection is dealt with more fully in another paper (fig. 11).

Conclusions.

(1) The substantia nigra is developed by a ventrolateral extension of cells from the characteristic mid-ventral proliferation in the basal lamina of the mesencephalon.

(2) It is first seen in the 22 mm. embryo as a peripheral crescentic strip of cells continuous with the ventrolateral angle of the mid-ventral proliferation.

(3) At the same time a narrow band of fibres appears on the superficial aspect of the nigral crescent. These are descending fibres from the cerebrum, and with the nigra they form the peduncle of the mid-brain.

(4) From the outset there is a close association between the substantia nigra and the descending cerebral pathway.

(5) By the 30 mm. embryo stage, the nigral crescent is separated into groups by the descending fibres. Characteristic medial and lateral groups are soon formed at the medial and lateral extremities.

(6) By the eleventh week (6·0 cm.) the nigra is disposed into two strata, corpus and cauda, the former lying deep to the latter with cerebral fibres between them. Medial, lateral and intermediate groups are recognizable in the corpus, and fibres extend between corpus and cauda and penetrate from the nigra into the cerebral pathway.

(7) In the 9·0 cm. fœtus the pyramidal shape of the substantia nigra is evident. The apex lies in the subthalamus and continues into the intermediate part of the corpus. This is soon flanked by the medial and lateral columns. The cauda lies along the ventral part of the nigra. The base is formed by the columns of the corpus and extends into the pons.

(8) At mid-term a new nigral stratum appears. It will be referred to as the caput. It lies on the dorsal aspect of the corpus and is separated from it by cerebral fibres. It links the medial and lateral groups of the corpus and projects aberrant groups into the tegmentum. The caput and cauda are present only in the mid-brain portion of the substantia nigra; the corpus extends to the subthalamus and pons.

(9) At the eighth fœtal month a rich plexus of fine myelinated fibres pervades the nigra, and fibres extend from it into the crus and tegmentum, and into the subthalamic nucleus.

(10) After birth the nigra retains its fœtal architecture, but enlarges and attains its maximum size in childhood.

(11) Minute black granules are first seen in some of the nigral neurones at mid-term. Thereafter they increase, but not all the neurones contain them. After birth granular cells are numerous.

(12) By dissection the pyramidal shape of the substantia nigra is confirmed.

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THE DEVELOPMENT OF THE HUMAN RED NUCLEUS AND CORPUS STRIATUM.

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I.—Red Nucleus.

Despite the functional importance of the extrapyramidal system, little is known of the origin of the red nucleus in the human subject. Frazer (1940) admits that "the actual mode of formation of the red nucleus is quite unknown." Shaner (1932) investigated the development of the mid-brain nuclei in pig embryos, but only from the 35 mm. stage. It seemed timely therefore to study the genesis of the mid-brain and diencephalic nuclei, and for this purpose a closely graded series of embryos and fœtuses was obtained ranging from 5 mm. to full term. The present paper is one of a series which records the formation of these nuclei.

In the embryo of 8·5 mm. length (4½ weeks), the mesencephalic portion of the neural tube exhibits roof plate, floor plate, alar (tectal) lamina, and basal lamina. Ependymal, mantle and marginal layers are already defined. Germinal cells of His are present in the ependymal layer, and ependymal proliferation gives rise to the congestion of cells which forms the mantle layer. From this congestion, cells spread peripherally and approach the marginal zone.

In the 10 mm. embryo (5 weeks), the basal lamina of the mid-brain is thicker than the other parts of the tube, and within its mantle layer a small concentration of cells is already defined on either side of the mid-line just under the ependyma. This concentration forms the somatic efferent column within which the oculomotor and trochlear nuclei arise (fig. 1).

Reference to fig. 1 shows a characteristic mass of cells in the mid-ventral portion of the basal lamina. This is produced by proliferation of peri-ependymal cells, and the direction of spread is ventral and ventrolateral. As the basal lamina thickens, the cavity is pushed dorsally since as yet there is no corresponding alar proliferation. In transverse sections the mid-ventral proliferation approaches the surface in the mid-line, while its lateral angles project into the basal lamina ventral to the circular group of cells representing the somatic efferent column. The marginal layer is

very narrow in the mid-ventral region, but widens somewhat near the lateral angles of the mid-ventral proliferation.

The mesencephalon in a 13 mm. embryo (5½ weeks) is oval from side to side as seen in transverse sections. The basal lamina is broader than at 10 mm., and the marginal zone is more clearly seen. The mid-ventral proliferation has created a median bulge towards the cavity, and this is flanked by two lateral ones corresponding to the oculomotor anlagen (fig. 2).

The posterior longitudinal bundle differentiates during the fifth week (13 mm.), and in transverse sections it is seen to be interposed between the somatic efferent nucleus and the wide marginal zone. The ventrolateral angle of the mid-ventral proliferation penetrates between the posterior longitudinal bundle and the marginal zone (fig. 2). In the marginal zone transverse fibres are recognizable. They originate in cells in the mid-ventral proliferation, and are regarded as simple commissural fibres (fig. 2). In the pons and medulla of this series, a corresponding mid-ventral proliferation and spread of cells is visible in the basal plate.

The mid-ventral proliferation of the basal plate at 19 mm. (6½ weeks) is invaded by transverse fibres (fig. 3). Previously similar fibres have been observed only in the marginal layer (*see above*). These new fibres appear to have attracted, displaced or transported some of the mid-ventral cells to a more lateral position in the basal lamina. A small group of cells is apparent at the visible extremities of these transverse fibres. Between this circular group of cells and the mid-ventral proliferation the fibres are clearly seen with chains of cells lying beside them. This round mass of cells lays the foundation of the red nucleus (fig. 3), and with the somatic efferent column creates the tegmentum of the mid-brain. Frazer (1940) states that it is frequently suggested that the red nucleus is derived from alar neuroblasts that have migrated ventrally. There does not seem to be any foundation for such an assumption in ontogenetic development.

The fibres associated with the red nucleus can be traced through the serial sections of a 19 mm. embryo to their origin in the cerebellar outgrowth. They form the brachia conjunctiva, and their decussation occurs among the cells of the mid-ventral proliferation of the mid-brain (fig. 4). Judging from this series it appears that the red nucleus arises by a migration of cells concurrently with the arrival of fibres in the mid-brain from the cerebellum. This finding is in agreement with Cajal's contention that "if, during embryonic development, new axons pass to some region of the central nervous system, ganglion cells may approach these axons either by sending forth long dendrites or by a migration of the cell body itself" (1892).

The comparative researches of Kappers (1913, 1916 to 17) also revealed movements of cells in relation to fibre tracts with which the cells have a functional relation, and from which they receive stimulation. His findings indicated that such cell movement is determined by a process of taxis or tropism, and he applied the term neurobiotaxis to the phenomenon. The doctrine of neurobiotaxis seems to have been widely accepted, and many examples supporting Kappers' thesis have been cited. It has been said, however, that there is as yet no experimental evidence that neurobiotactic movement occurs. Nevertheless, judging from observations in the present research, it seems reasonable to regard the genesis of the red nucleus as a neurobiotactic migration of cells towards fibres ascending from the cerebellum.

Search through the series of these early embryos did not reveal any fibres extending from the striate complex to the mid-brain. No reference therefore can be made to the relation between the anlage of the red nucleus and the striato-rubral fibres. Nor can it be ascertained what part these fibres play in the evolution of the red nucleus. It is possible, however, that both fibre systems (cerebello-rubral and striato-rubral) are concerned in the final orientation of the red nucleus.

Shaner (1932) studied the development of the red nucleus in pig embryos, but only recorded the appearances from the 35 mm. stage onwards. At that stage he "finds a thick tegmentum within which the red nucleus occurs as a loose lattice-work of neuroblasts extending from the roots of the oculomotor nerve to the habenulopeduncular tracts. Differentiation within the red nucleus begins with the appearance of large motor cells at the caudal pole of the red nucleus in the 35 mm. embryo." He recognized the dentato-rubral fibres in an embryo of 28 mm. length before either the dentate nucleus or the red nucleus had originated, but was able to trace them only as far as the ventral tegmental decussation. From the present research it is apparent that the anlage of the red nucleus is established at an earlier stage in the human embryo, and in relation to the entrance of cerebello-mesencephalic fibres (brachium conjunctivum) into the mid-brain.

In a transverse series of an embryo of 22 mm. length (7 weeks), the basal lamina is thicker than at earlier stages, and the aqueduct is much reduced in size (fig. 4). At the caudal extremity of the mid-brain the basal plate is occupied by an outstanding decussation of fibres that can be traced from their origin in the cerebellar outgrowth. They are the fibres of the brachia conjunctiva, and their decussation has completely displaced the cells of the mid-ventral proliferation (fig. 4). In the more cephalic sections

the decussation is less apparent, while the continuity between the cells of the red nucleus and those of the mid-ventral proliferation is definite.

A longitudinal series (7 weeks, 22 mm.) shows the entire red nuclear column. The basal plate of the mid-brain is short in length in comparison with the tectal plate owing to the mesencephalic flexure. Within the basal plate are two elongated concentrations of cells responsible for the protrusion of this area into the cavity. The dorsal column is the somatic efferent column. Ventral to this, but separated from it by the posterior longitudinal bundle, is the rubral column. This begins in the subthalamic region at an apex which soon swells into a spindle-shaped mass only to narrow and fade away in the lower part of the mid-brain. The component cells are differentiating neuroblasts, but no further change has occurred (fig. 12).

In the parasagittal sections of a 22 mm. embryo, the cerebello-mesencephalic fibres are visible in their entirety between the cerebellar outgrowth and the red nucleus. Both transverse and longitudinal sections at this period (seventh-eighth week, 22 to 29 mm.) reveal the fasciculus retroflexus passing from the habenular region through the medial part of the red nucleus to the ventral area of the mid-brain.

Towards the end of the second month of gestation the red nucleus is very obvious in the tegmentum. From the vicinity of the red nucleus a well-marked fibre tract can be followed rostrally to the hypothalamus. Here the mammillary complex is differentiating, and the tract is associated with its cells. It is recognized as the mammillo-tegmental tract (fig. 12). The somatic efferent column and the substantia nigra are well defined at this period (figs. 12 and 13).

The cerebello-mesencephalic fibre pathway (brachium conjunctivum) at this stage (29 mm., 8 weeks) exhibits a new feature in the form of a collection of cells situated among the fibres at the base of each cerebellar outgrowth (fig. 13). In the sagittal serial sections several smaller groups of cells occur along the length of the pathway. The largest group, incorporated within the cerebello-mesencephalic fibres at the root of the cerebellar lobe, subsequently develops into the dentate nucleus. The appearances suggest a continuity between the dentate anlage, the smaller groups of cells, and at a still more rostral position, the red nucleus. Later on there can always be seen in serial sections small groups of large cells among the decussating brachia conjunctiva. These may belong to the pars magnocellularis described as forming the caudal part of the red nucleus in the adult.

The generally accepted view of the origin of the dentate nucleus is

that it is derived from the mantle cells of the lateral cerebellar outgrowth, and that the dentate concentration appears at the end of the third fœtal month. Nevertheless the possibility of a tegmental origin is suggested by the appearances in the present research.

Like the oculomotor nucleus, the cells of the red nucleus show some arrangement into groups in the 4·0 cm. fœtus (9 weeks). The fibres reaching the red nucleus first encircle it forming a "capsule." As the fibres enter the nucleus they fan out, and the rubral cells are separated into groups adjacent to the capsule at the periphery of the nucleus, while scattered cells enmeshed in the entering fibres occupy the centre. So far the rubral cells show very little alteration from their spindle-shaped neuroblast state, whereas in the oculomotor nucleus typical small multipolar neurones are present.

At the tenth week (50 mm.) the nucleus ruber is larger and its groups of cells are better defined (*see* fig. 8 of paper on somatic efferent column). Enlargement of the cells is evident in the nucleus by the eleventh week (60 mm.).

It is interesting to note that during the third month of fœtal life, grouping of neurones is well marked in the oculomotor, rubral and nigral columns in the mid-brain. Various authors including Edinger (1908) and Brouwer (1918) have described functional localization within the groups of the oculomotor nucleus. Monakow (1895), Winkler and Potter (1914), and Rioch (1929 to 30) have identified and named component parts of the red nucleus in lower mammals. Hatschek (1907) recognized magno-cellular and parvo-cellular portions, and showed that the former predominates in lower animals and the latter becomes more conspicuous in higher forms. Mingazzini (1928) identified these two divisions in man, the large-cell part being caudal to the small-cell part. The rubrospinal tract arises in the caudal magno-cellular part. Davenport and Ranson (1930) could not identify a rostral small-cell part in the red nucleus of the cat or rabbit. These authors state furthermore "we have been unable to see any advantage gained by subdivisions of the red nucleus other than a compact (caudal) and a diffuse (rostral) part."

It has not been possible to determine how far the grouping of the neurones in the red nucleus in the early developmental stages compares with the organization in the adult. Oculomotor nerve-fibres and the fibres of the fasciculus retroflexus pass through the red nucleus on their way to the interpeduncular region and they may displace some of the rubral cells. Davenport and Ranson (1930) drew attention to this appearance.

By the fourteenth week (9·0 cm.) larger and smaller neurones are recognizable in the red nucleus. These may be the precursors of those found respectively in the so-called magno-cellular and parvo-cellular portions of the adult red nucleus. Owing to the increasing size of the crus, the red nucleus now appears more deeply situated in the tegmentum.

The nucleus ruber is outstanding from 7·0 cm. (12 weeks) onwards (fig. 6). It is encircled by the "capsule" formed by entering fibres, and the arrangement of cell groups at the periphery is characteristic. According to Papez and Stotler (1940) different portions of the red nucleus give origin to efferent rubral fibres which form the rubro-oculomotor, rubro-reticular and rubrospinal tracts. The rubro-oculomotor tract contributes fibres to the oculomotor, trochlear and possibly the abducent nuclei. The fibres of the rubrospinal tract probably end in relation to the motor cells of the spinal cord. Papez and Stotler (1940) suggest that "if these facts are correct, the inference is that a part of the red nucleus regulates movements of the eye muscles." From the findings in the present research it is suggested that the neuronal groups evident in the fœtal red nucleus develop into the adult portions described by Papez and Stotler (1940). In that case the rubral groups might ultimately become related to specific muscle groups or muscles. It is known that functional localization occurs within the groups of the oculomotor nucleus. The same may be true of the groups of the red nucleus.

In some of the fœtal specimens at mid-term the cell groups in the red nucleus occur chiefly in the dorsal and ventral regions. The neurones are now well developed and similar to those of the substantia nigra, but the oculomotor cells are still larger than any others. Fine dark-brown granules are present in both the nigral and rubral neurones at this period. They are disposed at the periphery of the cells. Large multipolar neurones occur among the decussating fibres of the dentato-rubral pathway. Reference to this point has been made earlier.

By the Weigert-Pal technique it was found that at the twenty-third week (18 cm.) the fibres of the brachia conjunctiva were finely myelinated. In Keene and Hewer's series this appearance was apparent at the twenty-sixth week (21 cm.) (1931-32). The fibres are heavily medullated by the eighth fœtal month.

During the last months of fœtal life the red nucleus increases steadily in size, but otherwise no great change is evident. The neurones continue to be arranged in groups, mainly at the periphery near the "capsule," while the centre is occupied by fibres and dispersed cells. Fibres running across the nucleus constitute the lamina medullaris nuclei rubris. Frequently a

lateral prominence from the red nucleus is present, and large multipolar neurones are entangled among the fibres of the capsule. Davenport and Ranson (1930) noticed a lateral cell aggregation adjacent to the red nucleus of the cat and rabbit.

In the early post-natal period the nucleus ruber enlarges rapidly and its neurones contain a diffuse brownish substance. By the fifth year the nucleus appears to have reached its full size. Frequently a circle of blood vessels accompanies the "capsule." Brownish coloration of many of the rubral neurones occurs but never appears in the form of coarse granules so characteristically seen in the nigral neurones. Larger and smaller neurones are coloured, but by no means all of them.

During the enlargement of the nucleus in later fœtal life, infancy and childhood, the arrangement of its neurones into groups becomes less obvious than in earlier fœtal life, owing, no doubt, to their dispersal by the progressive influx and myelination of fibres. Although peripheral grouping is evident in the adult red nucleus it never appears to be so constant and specific as that in the substantia nigra and the oculomotor nucleus.

II.—The Corpus Striatum.

Owing to the functional relationship between the red nucleus and the corpus striatum, the development of the latter was examined. In the embryo of 8·5 mm. total length (4½ weeks) two small lateral vesicles have arisen from the fore-brain. Already a thickening of the lateral wall is seen in each, produced by proliferation of peri-ependymal cells and consequent increase in the width of the mantle layer. In the 10 mm. embryo (5 weeks) the thickening of the wall of the lateral outgrowth (cerebral hemisphere) has spread towards the floor (fig. 14). Here it meets the alar enlargement of the diencephalon which becomes the thalamus. The thickening of the wall of the cerebral hemisphere is the anlage of the corpus striatum, and a recognizable depression between it and the thalamus marks the future stria terminalis.

By the sixth week (19 mm.) the cerebral vesicle is larger and the striate mass acquires a more ventral position, appearing in the floor of the vesicle level with the thalamic enlargement.

At 22 mm. (7 weeks) the cerebral vesicles have further enlarged and now overhang the hypothalamic and subthalamic portions of the diencephalon (fig. 15). In the subthalamus the corpus subthalamicum of Luys is defined, and the proliferation of cells in the mid-ventral region of the diencephalon indicates the differentiation of the mammillary complex.

The lowest part of the cerebral vesicle becomes the descending horn, and already the corpus striatum is bulging into it.

In this series, stratification of the wall of the cerebral hemisphere has commenced, and two cellular strata, separated by fibre layers, are distinguishable. From the cells in these strata fibres issue and collect between the corpus striatum and the thalamus (fig. 15). A corona radiata is formed and then the fibres become concentrated into a bundle which can be traced towards the subthalamus where it proceeds on the superficial aspect of the corpus subthalamicum towards the mid-brain. These fibres map out the position of the internal capsule, and for the time being will be referred to as the descending cerebral fibres. In the sagittal sections of a 22 mm. embryo the fibres are traceable from the subthalamic region along the ventral aspect of the mid-brain, pons and medulla.

As they descend, the cerebral fibres pass not only between the corpus striatum and the thalamus, but also through the corpus striatum. In this position they define two parts in the striate mass, medial and lateral. The medial portion retains its relationship to the cavity of the vesicle and becomes the caudate nucleus. The lateral part is separated from the cavity by the fibres, but maintains continuity with the lateral wall of the cerebral vesicle. It is the lentiform nucleus, and it approaches the surface on the lateral aspect of the vesicle, only to be depressed by the growth of the opercula at a later date (fig. 15). Frazer (1940) describes the demarcation of the corpus striatum into caudate and lentiform nuclei during the latter part of the third month.

A longitudinal series of sections through the brain of a 29 mm. embryo (8 weeks) (fig. 13) shows proximally the internal capsule interposed between the (medial) ventricular part of the corpus striatum (i.e. the caudate nucleus) and the (lateral) non-ventricular part (the lentiform nucleus). Just behind, the internal capsule occupies the interval between the striate body and the thalamus.

By the end of the twelfth week of fœtal life (7·0 cm.) the caudate and lentiform nuclei of the corpus striatum are clearly separated by fibres originating in cells of the cerebral vesicular wall (now designated cerebral cortex), and forming the internal capsule (fig. 16). Furthermore the lentiform nucleus is divided into three parts comprising the globus pallidus and the putamen. Frazer (1940) describes the demarcation of the striate body into caudate and lentiform portions during the third fœtal month, but makes no reference to the age at which the subdivision of the lentiform nucleus occurs.

The study of the corpus striatum was not carried beyond this stage when all its component parts have been laid down.

Conclusions.

(1) The human red nucleus develops as a migration of cells from the mid-ventral proliferation of the mesencephalic basal lamina.

(2) These cells migrate towards, and become associated with, cerebello-mesencephalic fibres (brachia conjunctiva) which reach the mid-brain in the embryo of 19 mm. length (6½ weeks).

(3) A collection of cells, situated among the cerebello-mesencephalic fibres at the base of the cerebellar outgrowth, is seen in the 29 mm. embryo (8 weeks). These cells develop into the dentate nucleus which appears in series with the red nucleus and is linked to it by tiny groups of cells in the dentato-rubral (cerebello-mesencephalic) fibre pathway. The possibility of a tegmental origin of the dentate nucleus is suggested.

(4) Grouping of neurones in the red nucleus begins in the 4·0 cm. fœtus (9 weeks).

(5) Minute brown granules appear in the rubral neurones at mid-term. Later a diffuse brown coloration distinguishes the cells.

(6) The corpus striatum arises as a thickening of the lateral wall of the cerebral vesicle in the 10 mm. embryo (5 weeks).

(7) In the 22 mm. embryo (7 weeks) descending cerebral fibres separate the corpus striatum into medial (caudate) and lateral (lentiform) parts.

(8) In the 7·0 cm. fœtus (12 weeks) the lentiform nucleus is subdivided into putamen and globus pallidus.

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LEGENDS FOR PLATES I to VI (see over)

FIG. 1.—Mesencephalon. 10 mm. embryo. ×30.

FIG. 2.—Mesencephalon. 13 mm. embryo. ×30.

FIG. 3.—Tegmental region of mesencephalon. 19 mm. embryo. ×85.

FIG. 4.—Mesencephalon. 22 mm. embryo. ×25.

FIG. 5.—Peduncle of mid-brain. 6·0 cm. fœtus. ×25.

FIG. 6.—Mid-brain. 7 cm. fœtus. ×8.

FIG. 7.—Mid-brain. Mid-term. ×10.

FIG. 8.—Bundles of cerebral fibres within the substantia nigra. 6 months' fœtus. ×160.

FIG. 9.—Processes of nigral neurones ramifying among cerebral fibres in the crus. Full-term fœtus. ×300. (Cajal's silver technique.)

FIG. 10.—Dissection to expose the substantia nigra. a = apex; b = base. (Dissected by Frank Howarth, M.B., Ch.B.)

FIG. 11.—Fibre connections between the optic tract and the substantia nigra and the subthalamic nucleus. 19·5 cm. fœtus. ×30.

FIG. 12.—Pars tegmentalis (basalis) of mesencephalon; parasagittal section. 22 mm. embryo. ×25.

FIG. 13.—Parasagittal section of entire brain. 29 mm. embryo. ×10.

FIG. 14.—Fore-brain. 10 mm. embryo. ×18.

FIG. 15.—Fore-brain. 22 mm. embryo. ×15.

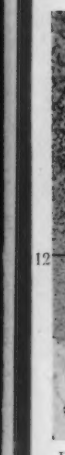
FIG. 16.—Coronal section of brain. 7·0 cm. fœtus. ×8.

KEY TO ILLUSTRATIONS.

1.—Alar lamina.
2.—Mantle layer.
3.—Marginal layer.
4.—Basal lamina.
5.—Mid-ventral proliferation.
6.—Lateral angle of (5).
7.—Somatic efferent column (oculomotor nucleus).
8.—Posterior longitudinal bundle.
9.—Oculomotor nerve.
10.—Transverse fibres in the marginal zone.
11.—Brachium conjunctivum (cerebello-mesencephalic fibres).
12.—Red nucleus.
13.—Descending cerebral fibres (crus).
14.—Substantia nigra.
15.—Corpus of substantia nigra.
16.—Cauda of substantia nigra.
17.—Lateral group of corpus.
18.—Medial group of corpus.
19.—Intermediate group of corpus.
20.—Caput of substantia nigra.
21.—Accessory group of substantia nigra.
22.—Nigral neurones and processes issuing from them.
23.—Peduncle.
24.—Interpeduncular space.
25.—Trochlear nerve.
26.—Somatic efferent column (trochlear nucleus).
27.—Mammillo-tegmental tract.
28.—Mammillary concentration.
29.—Thalamus.
30.—Anlage of dentate nucleus.
31.—Group of neurones in brachium conjunctivum.
32.—Optic tract.
33.—Optico-nigral fibre connection.
34.—Optico-subthalamic fibre connection.
35.—Subthalamo-nigral fibres.
36.—Subthalamic nucleus.
37.—Caudate nucleus.
38.—Internal capsule.
39.—Lentiform nucleus.
40.—Stria terminalis.
41.—Hypothalamus
42.—Pituitary anlage.
43.—Anlage of corpus striatum.
44.—Cerebral hemisphere.
45.—Putamen.
46.—Globus pallidus.

(The use of a hand lens is recommended in examining the photographs.)

F



To

PLATE I.

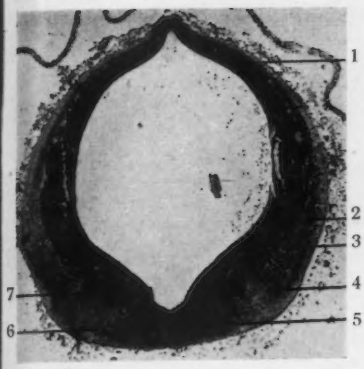


FIG. 1

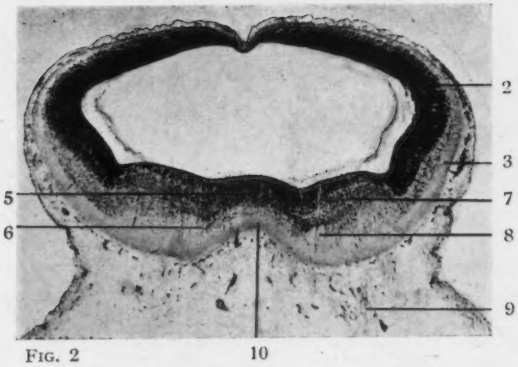


FIG. 2

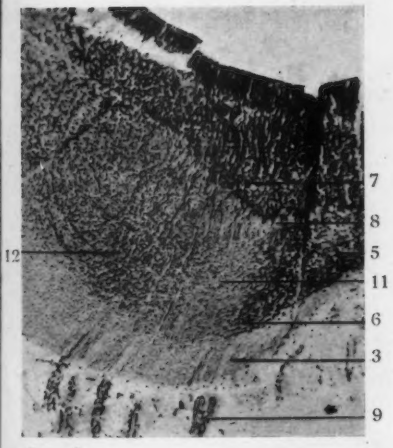


FIG. 3

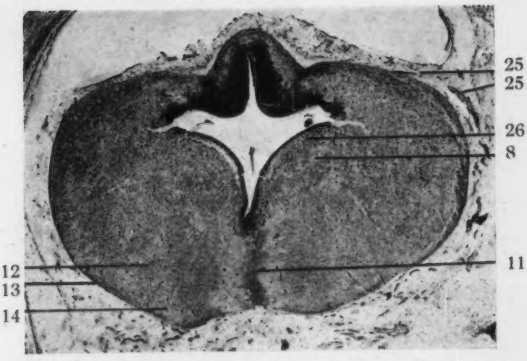


FIG. 4

To illustrate article by E. R. A. Cooper.

PLATE II

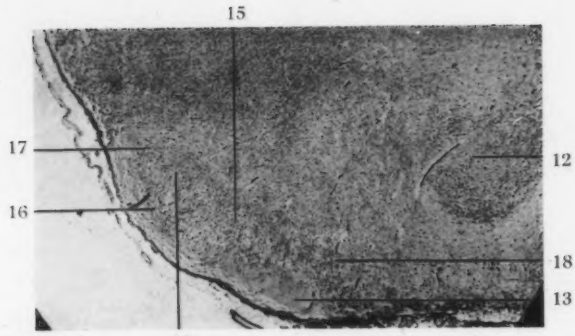


FIG. 5

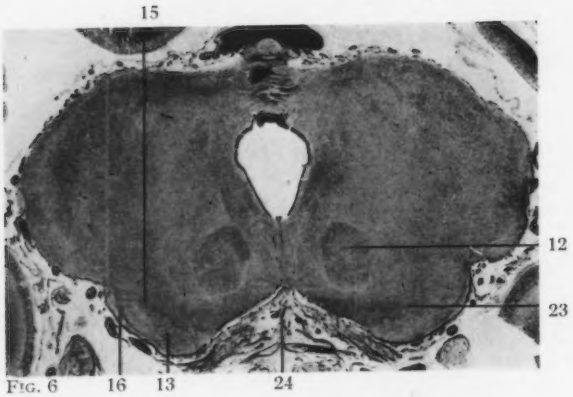


FIG. 6

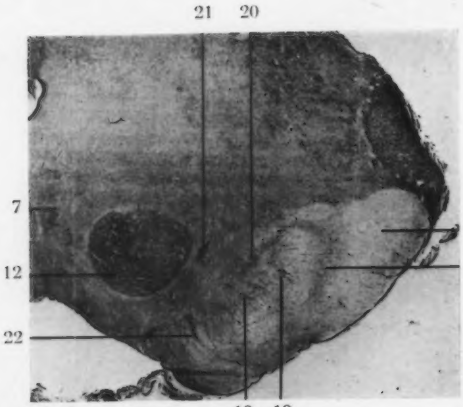


FIG. 7

To illustrate article by E. R. A. Cooper.

PLATE III.

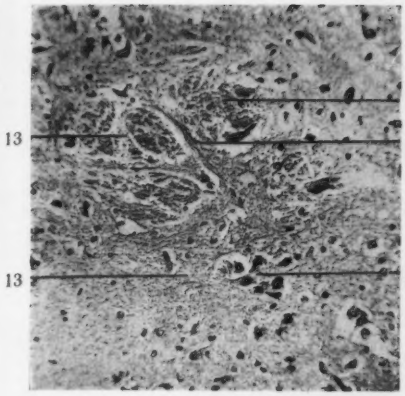


FIG. 8

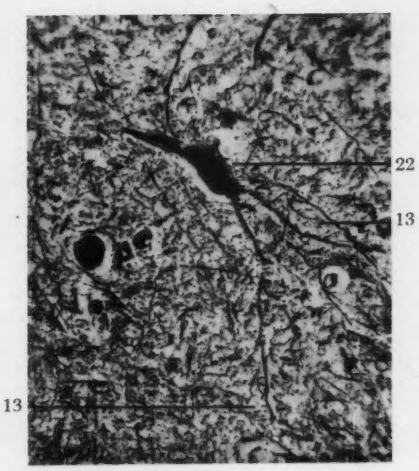


FIG. 9

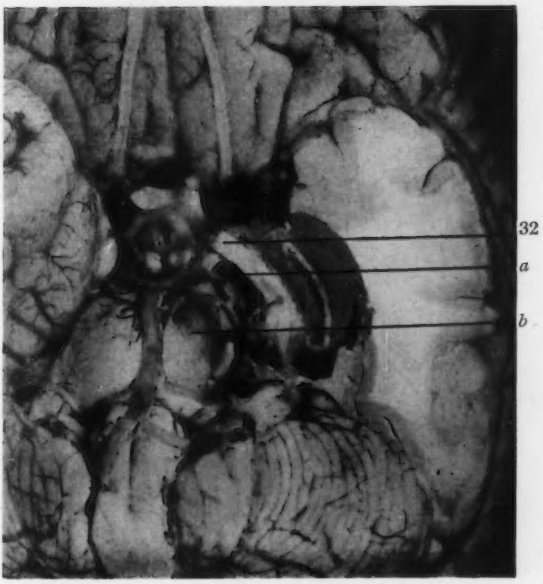


FIG. 10

To illustrate article by E. R. A. Cooper.

PLATE IV.

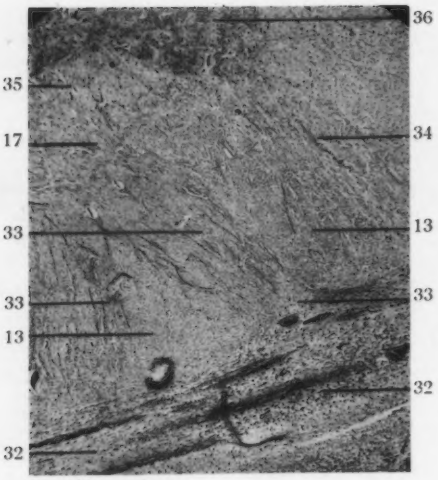


FIG. 11

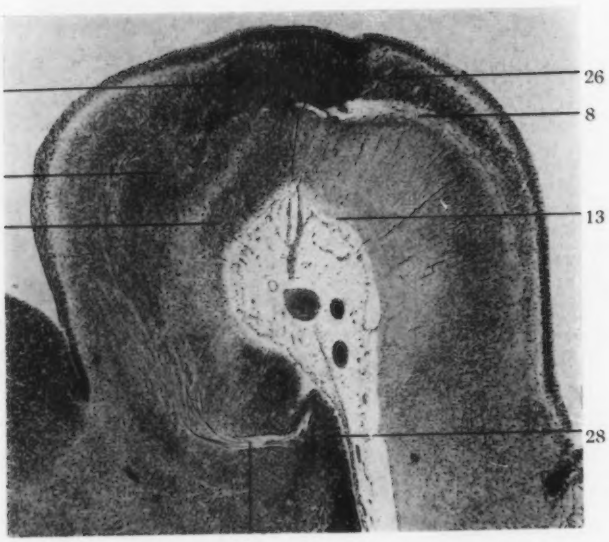


FIG. 12

To illustrate article by E. R. A. Cooper.

PLATE V.

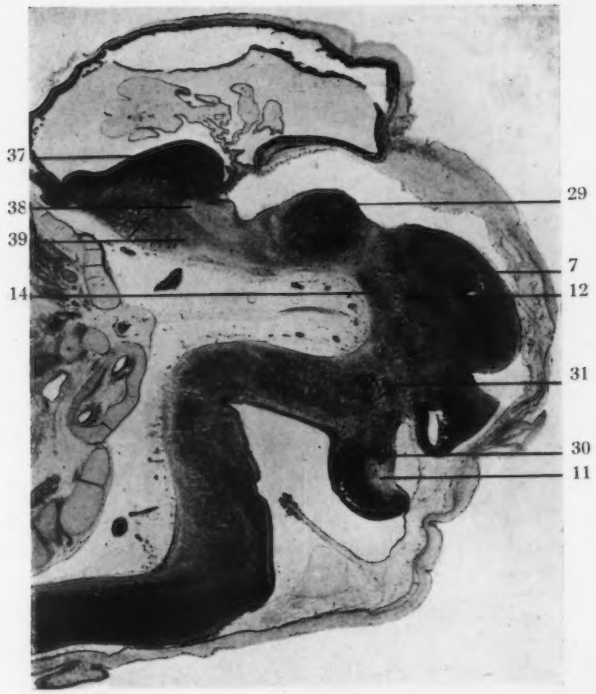


FIG. 13

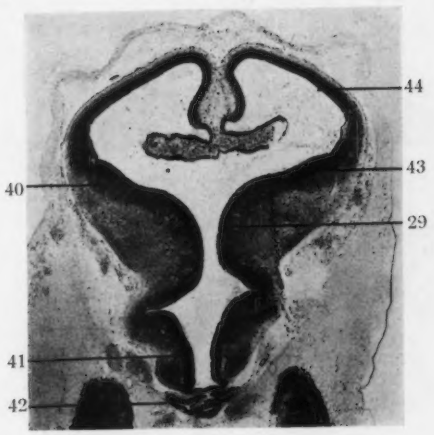


FIG. 14

To illustrate article by E. R. A. Cooper.

PLATE VI.

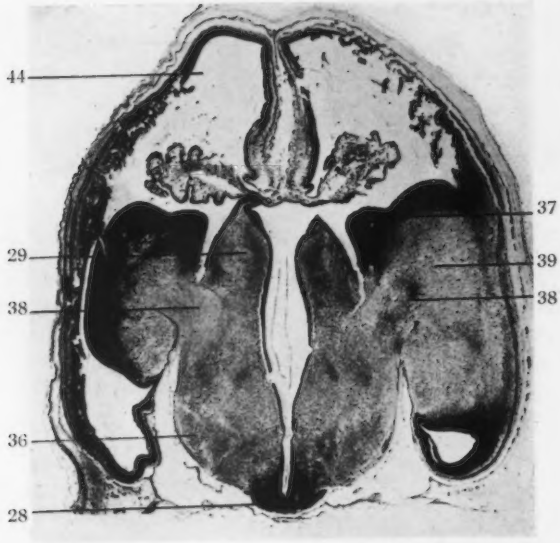


FIG. 15

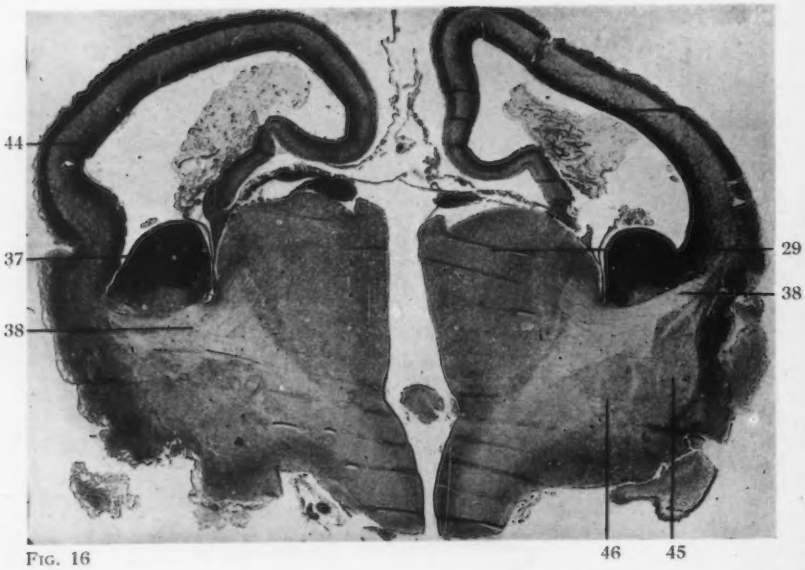


FIG. 16

To illustrate article by E. R. A. Cooper.

ACCESSORY OPTIC TRACTS IN THE HUMAN FŒTUS.

BY E. R. A. COOPER.

Department of Anatomy and Histology, University of Manchester.

In investigating the development of the lateral geniculate body the course of the optic tract naturally came under review. It is generally agreed that the majority of the tract fibres end in the dorsal nucleus of the lateral geniculate body, 70% estimated by Bernheimer (1899), and 80% claimed by von Monakow (1905). The remainder proceed to the superior colliculus (Bernheimer, 1899; Minkowski 1923-24), and, according to certain authors, to the pulvinar of the thalamus (Pavlow, 1900; Probst, 1900; Winkler, 1911; Minkowski, 1923-24), and to the pretectal nucleus (Lashley, 1934). Opinions vary regarding the distribution in the pulvinar and pretectal nucleus, but it is no part of this paper to discuss this point.

In conjunction with the main optic tract, two accessory optic tracts are known to occur in certain animals. These are named: (1) the tractus accessorius optici posterior of Gudden (1881); (2) the fasciculus accessorius optici anterior of Bochenek (1908).

The tractus accessorius optici posterior is referred to sometimes as the basal optic root or tract (tractus opticus basalis), and the tractus peduncularis transversus (Marburg, 1903). It was first revealed by Gudden (1881), and he confirmed its connection with the eye. It is described as arising in retinal cells and accompanying the main optic tract as far as the lateral geniculate body. Here it leaves the main optic tract and turns ventrally, passing over the superficial aspect of the peduncle towards the interpeduncular space. Reaching the medial aspect of the peduncle it enters a collection of cells (nucleus tractus peduncularis transversi) lying adjacent to the medial part of the substantia nigra. Connections with the substantia nigra at this position are said to be effected. According to Clark (1942), there is evidence that this tract exists in several lower animals, and experimental work has confirmed its presence in the rabbit (Loepp, 1912; Pavlow, 1900), guinea-pig (Wallenberg, 1904; Frey, 1937), rat (Clark, 1942; Lashley, 1934), opossum (Bodian, 1937), and in the phalanger (Packer, 1941). Bochenek (1908) also described the posterior accessory tract in the rabbit, and Tsai (1925) found it in the opossum.

On the other hand Clark (1942) states that "there is considerable doubt whether the posterior accessory optic tract is present in the brain of higher mammals." Gillilan (1941), however, states that it exists in the cat and monkey, but Clark (1942) is not convinced by this author's conclusions. He points out that investigations of these accessory tracts have been made on "normal histological material which is liable to misinterpretation, for it does not permit the assumption that the fibres seen in the position of the so-called accessory optic tracts are really retinal in origin."

Bochenek (1908) identified in the rabbit a hitherto unknown tract which he called the fasciculus accessorius optici anterior. This bundle "consists of crossed fibres and occupies the hindmost position in the chiasma at the base of the brain. When the main optic tract travels dorsolaterally, the accessory tract remains on the base of the brain and reaches the position between the peduncle and the grey matter of the infundibular region. Next the accessory tract runs dorsally amongst the bundles of the peduncle to the dorsal aspect of the peduncle where it ends in the posterior part of the corpus subthalamicum."[1]

The presence of the anterior accessory optic tract has been confirmed in the rabbit (Pavlow, 1900; Loepp, 1912) and in rodents (Gillilan, 1941). Others have failed to identify it in the opossum (Bodian, 1937), cat (Barris, Ingram and Ranson, 1935) and ferret (Jefferson, 1940). Barris, Ingram and Ranson (1935) conclude that the anterior accessory optic tract does not exist in higher mammals, and Gillilan (1941) was unable to distinguish it in carnivora or primates.

Little is known regarding the accessory optic tracts in the human subject. Frey (1937) recognized the posterior accessory optic tract in a human embryo but the stage cannot be ascertained.[2]

During an investigation of the development of the substantia nigra in the human subject, it was observed that, in some fœtal cases, fibres left the optic tract and took a transpeduncular course dorsally. Bearing in mind the knowledge regarding the accessory optic tracts, and the occurrence of aberrant fibres in the chiasma, the position of these transpeduncular fibres was carefully examined. The possibility of optic fibres reaching the substantia nigra directly had been conjectured. Sterzi (1914-15) has described fibres extending into the substantia nigra from the posterior accessory optic tract.

In a specimen at the sixth fœtal month (19·5 cm.) a band of fibres was observed (in serial sections cut in the plane of the optic tract) to leave the

[1] The author is indebted to Dr. W. Schlapp for this translation.
[2] The author has been unable to procure this reference.

optic tract as it approached the lateral geniculate body. The band passed dorsally through the peduncle and joined the lateral group of neurones of the corpus of the substantia nigra (fig. 1). The band is regarded as a nigral connection since nigral neurones are present within it as it joins the lateral nigral group. It will be referred to as an optico-nigral connection. Other fibres slightly farther along the optic tract were seen to run parallel to the optico-nigral band and to pass through the crus into the subthalamic nucleus (fig. 1). Metallic impregnations revealed that the subthalamic nucleus is closely linked by fibres to the substantia nigra. Rioch (1929-30) has described a subthalamo-nigral pathway.

At other fœtal stages further examples of a direct transpeduncular link between the optic tract and the substantia nigra, and between the optic tract and the subthalamic nucleus, were observed (figs. 2 and 3). In most cases the optico-nigral intercommunication was between the optic tract and the lateral group of the corpus of the substantia nigra, but sometimes the medial group of the nigral corpus was involved. In all cases, however, the connection was with the phylogenetically older part of the substantia nigra (paleo-nigrum).

Sterzi (1914-15) traced fibres of the tractus peduncularis transversus (posterior accessory optic tract) directly into the substantia nigra. Gillilan (1941) refers to the "tractus optico-nigralis" consisting of fibres of the posterior accessory optic tract which have pursued a long course over the surface of the peduncle to the medial aspect of the substantia nigra. According to this author the fibres entering the nigra are of retinal origin. The present research shows that optico-nigral fibres have been identified in the human fœtus, but that the course is a short direct transpeduncular one from the optic tract to the substantia nigra. In this investigation it has not been possible to determine the source of all the fibres within the optic tract.

In his review (1942) Clark suggests that in the optic tract certain hypothalamic commissures (supra-optic commissures) are difficult to distinguish from retinal fibres. He states that these commissural fibres have nothing to do with vision; and that there are aberrant fibres in the chiasma which the "casual observer may mistake for terminal optic fibres." Three supra-optic commissures are well known, the dorsal commissure of Meynert, Gudden's commissure and Ganser's commissure. Rioch (1929-30) found that in the dog the anterior accessory tract of Bochenek accompanies Meynert's commissure to the corpus subthalamicum and zona incerta. It is doubtful whether Gudden's commissure exists in man. Tsai (1925) describes some connections between Ganser's commissure and the sub-

thalamic nucleus, while Rioch (1929-30) believes that in the dog this commissure is related to certain hypothalamic elements. None of these authors refer to any connections between the supra-optic commissures and the substantia nigra. It is therefore maintained that certain fibres pass from the optic tract directly to the substantia nigra. It is believed that these fibres do not belong to the supra-optic commissures.

An indirect connection between the optic tract and the substantia nigra has also been observed. Fibres from the optic tract were traced through the peduncle (transpeduncular) to the subthalamic body (figs. 1-3). These fibres occur in the position of the anterior accessory tract of Bochenek and they enter the corpus subthalamicum on its ventral aspect. From the cells in the latter, fibres proceed into the substantia nigra which lies ventro-caudal to the corpus subthalamicum. This would indicate an alternative route, whereby certain fibres present in the optic tract are brought into relationship with the substantia nigra.

Thus it is maintained that the present study has revealed in the human fœtus:

(1) The occurrence of a direct fibre connection between the optic tract and the substantia nigra.

(2) The presence of a tract similar in its disposition to that described by Bochenek (1908) in rabbits as the anterior accessory optic tract. It runs from the optic tract through the peduncle to the subthalamic body.

(3) An indirect optico-nigral connection via the subthalamic nucleus.

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PLATE VII.

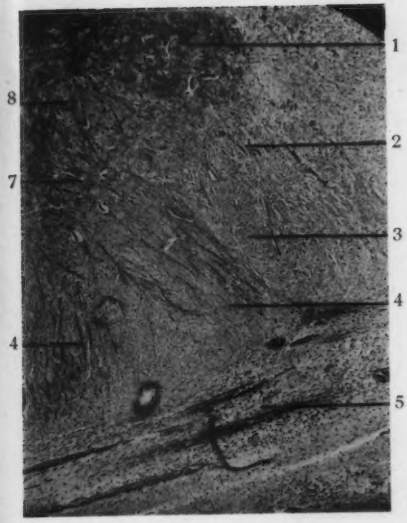

FIG. 1

FIG. 2

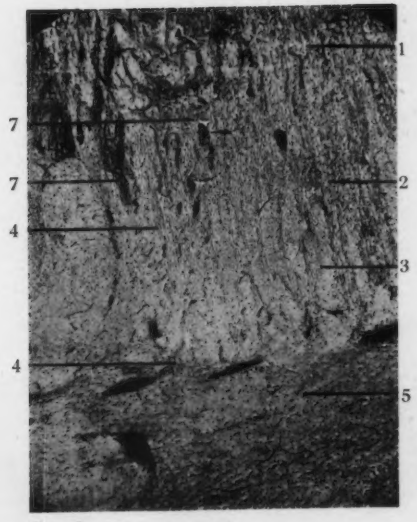

FIG. 3

To illustrate article by E. R. A. Cooper.

PAVLOW, M. (1900), *Le Nevraxe*, **1**, 235.
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LEGENDS.

FIG. 1.—The optic tract and the substantia nigra and subthalamic body of Luys. 19·5 cm. fœtus. ×30.

FIG. 2.—Subthalamic region. 16 cm. fœtus. ×30. Cajal's silver technique.

FIG. 3.—Optico-nigral and optico-subthalamic connections. 8 months' fœtus. ×30.

KEY TO ILLUSTRATIONS.

1.—Subthalamic nucleus.
2.—Optico-subthalamic fibres.
3.—Cerebral fibres of the peduncle.
4.—Optico-nigral fibres.
5.—Optic tract.
6.—Lateral geniculate body.
7.—Nigral neurones.
8.—Subthalamo-nigral connections.

THE DEVELOPMENT OF THE NUCLEI OF THE OCULOMOTOR AND TROCHLEAR NERVES (SOMATIC EFFERENT COLUMN).

BY E. R. A. COOPER.

Department of Anatomy and Histology, University of Manchester.

THIS investigation of the origin of the somatic efferent column in the human subject has been carried out in a closely graded series of embryos and fœtuses. It forms part of a general survey of the differentiation of mesencephalic and related nuclei including the lateral geniculate body.

A good deal of literature exists regarding the grouping of neurones in the somatic efferent column, and the functional aspect of this grouping. The works of Perlia (1889) and Brouwer (1918) are well known, and more recently Hunter (1923) and Clark (1925-26) have dealt with the oculomotor nucleus in lower mammals. Mann (1926-27) investigated the development of the human oculomotor nucleus, and Pearson (1943) described the origin of the trochlear nerve in fœtuses, while Windle's papers (1932) refer to cat embryos.

Although the ultimate findings in the present research correspond with those of other workers, it was felt that still another description was warranted, since it relates the development of the somatic efferent column from so early a stage in human embryology.

The earliest embryo examined was 5 mm. long, in age about three weeks. At this stage fore-, mid- and hind-brain vesicles are differentiated. The mid-brain is recognized in transverse sections by its continuity with the diencephalon (with optic outgrowths) in front, and by the widening of its cavity at the commencement of the pons behind. In length it measures only 0·2 mm. The neural tube already exhibits alar and basal laminæ, and in the mesencephalon the interlaminar sulcus is well marked. Ependymal, mantle and marginal layers are defined. Within the ependymal zone are germinal cells of His in which the nuclei exhibit mitotic phases. All the other cells appear to be simple undifferentiated (indifferent) cells and they are disposed in syncytial fashion.

Transverse sections of an 8·5 mm. embryo (4½ weeks) show that in the mid-brain the basal lamina is thicker than the alar lamina owing to proliferation of cells, and it forms a bulge on either side of the mid-ventral line. The two ventral bulges encroach on the cavity which is

reduced in size and occupies a more dorsal position. Within each basal bulge the mantle layer is demarcated into an inner zone of closely approximated cells, and an outer zone of more dispersed cells. The former will be referred to as the "zone of congestion," and the latter as the "zone of spread" (fig. 1). The zone of congestion seems to arise as a result of rapid ependymal and peri-ependymal cell multiplication. Some of the cells spread peripherally and form the zone of spread and thus enlarge the tube. Processes from the cells in the latter zone can be traced still more peripherally where they become entangled and form a fibrillary marginal zone. These cells are regarded as neuroblasts. Other smaller cells, better seen in the peripheral regions, are beset with many processes and are recognized as glial elements. Germinal cells of His are visible in the ependymal zone.

In the transverse sections of the mid-brain of a 10 mm. embryo (5 weeks), each basal bulge presents a defined circular collection of cells in the mantle layer. It is the first grouping of neuroblasts to be identified, and it is vascularized by vessels penetrating from the surrounding mesoderm. Congestion and spread of neuroblasts are apparent in the circular mass, and the cell processes are directed ventrally. The circular group is regarded as a section across the somatic efferent column which proximally becomes the oculomotor nucleus, and distally the trochlear nucleus (fig. 2). Some fibres are seen to proceed from the nuclear mass towards the alar region of the mid-brain. They are recognized as fibres of the trochlear nerve. Other fibres are directed ventrally and become the fibres of the oculomotor nerve, but none of them have reached the surface at this stage.

Another feature in this series (10 mm.) is a rich cell accumulation in the mid-ventral region of the basal lamina. A characteristic mass of neuroblasts is formed from which there is a spread in the ventral and ventrolateral directions (fig. 2). This mid-ventral proliferation and spread of cells further widens the basal lamina, and the cavity and somatic efferent column are seen to occupy a more dorsal position. Germinal cells of His are present in the ependymal zone, but elsewhere no mitoses could be detected among the cells in the mid-ventral region. According to Maximow and Bloom (1942), as soon as neuroblasts have differentiated from the indifferent cells of the neural tube, they appear to lose the power of multiplication. This may be one explanation why mitotic figures are not recognizable. On the other hand Kappers (1932) asserts that "division in young neuroblasts under normal circumstances is always mitotic." Cajal (1928) states that "in the course of prolonged investigations in

mammals we have never seen a case of indubitable neuronal division." Among these conflicting views the possibility of direct division of young neuroblasts must not be overlooked. Cowdry (1924) states that "there are so many indications of the process (of amitosis) in older tissue cultures, that it is hard to believe that it does not occur more frequently than the observations on living cells would seem to indicate." In Keibel and Mall's "Embryology" (1910) one reads "whether the proliferation of the nuclei of the mantle layer is always mitotic, or whether it is to some extent amitotic, remains to be determined."

At 13 mm. (5½ weeks) processes from the cells in the rostral part of the somatic efferent column are seen in serial sections to emerge from the ventrum of the mesencephalon (fig. 3). Here they collect together and form the oculomotor nerve. Thus the cephalic and greater part of the somatic efferent column becomes the oculomotor nucleus. In the caudal region of the mesencephalon, the fibres can be traced from the somatic efferent cells dorsally into the alar lamina. It is obvious that this part becomes the trochlear nucleus, but at this age the trochlear fibres cannot be followed beyond the alar region.

The oculomotor and trochlear column is better defined at 13 mm. (5½ weeks), since it is now demarcated on its ventral aspect from the marginal zone by a bundle of fibres. These are cut across in the transverse sections, indicating that they pursue a longitudinal course. The bundle is identified as the posterior longitudinal bundle (fig. 3), and the close proximity of it to the somatic efferent column is apparent from the outset. Keene and Hewer (1931-32) identified the posterior longitudinal bundle in a 12 mm. human embryo and the present research is in agreement. The establishment of the somatic efferent column thus appears to be related to the formation of the posterior longitudinal bundle.

The distinction between the oculomotor and trochlear portions of the somatic efferent column can only be recognized by the direction of the fibres arising from its component cells. The cells are identical in both portions, being pyriform with one process emerging from the narrow end; but clear definition of the cells is not always apparent owing to their close concentration.

In an embryo of 16 mm. (6 weeks), the trochlear fibres can be followed through the alar region to their decussation in the mid-dorsal position and their emergence from the dorsum of the lowest part of the mesencephalon. The alar plate exhibits proliferation with congestion of its cells. The trochlear fibres approaching their decussation penetrate among these cells, some of which accumulate at the periphery where they become concen-

trated into a mass on either side of the mid-dorsal line. It is found that these cells subsequently create the tectum (fig. 4).

Advance in the development of the oculomotor nucleus is evident in the 19 mm. embryo (6½ weeks). Some of its cells exhibit a better definition within the somewhat syncytial concentration, and their nuclei are larger. A median group of cells, belonging to the mid-ventral proliferation (*see* above), is now seen to join the right and left oculomotor nuclei together. These median cells become Perlia's median nucleus and they are similar to those in the oculomotor nuclei. They are distinguished from the other cells of the mid-ventral proliferation by the larger size of their nuclei. They emit well-defined processes which proceed ventrally to join those issuing from the lateral oculomotor nuclei. Thus the oculomotor complex at 19 mm. consists of two lateral parts united by a median part (fig. 5). In Mann's series this arrangement was first seen in a 35 mm. embryo (1926-27).

In an embryo of 22 mm. (7 weeks) sectioned transversely, the oculomotor complex presents similar features, but the cell nuclei are paler and exhibit chromatin spots. The trochlear nucleus is identified in the caudal part of the mesencephalon. It appears as a crescentic mass of cells which bulges the ependyma of the basal lamina into the cavity. The cells are similar to those in the oculomotor nucleus and their processes pass through the alar region, decussate in the mid-dorsal position, and emerge somewhat laterally (fig. 6).

A series in which the embryo was sectioned longitudinally shows the relative proportions of oculomotor and trochlear parts of the somatic efferent column at 7 weeks (22 mm.). The proximal two-thirds form the oculomotor nucleus (lateral or main part) and it is spindle-shaped. The distal one-third is the trochlear nucleus and it tapers to an apex at the isthmus rhombencephali. By this age the somatic efferent nuclei occupy the dorsal part of the tegmentum of the mesencephalon, the foundations of the columns of the red nucleus and substantia nigra having differentiated in the ventral part (*see* fig. 6).

At the end of the second month of gestation (29-30 mm.) the oculomotor complex still consists of three groups (two lateral and one median) composed of medium sized cells, surrounded by small cells. Each lateral group is regarded as the main nucleus. The larger cells possess pale nuclei with prominent nucleoli, and cytoplasm of visible amount but ill-defined limits, as it merges at the angles into that of adjacent cells. Some idea of the size is obtained by comparison with red blood corpuscles; the nuclei are slightly larger than the corpuscles. The oculomotor cells can now

be regarded as young neurones, and they are much further advanced than the cells in the rubral or nigral columns. The trochlear nucleus at this stage appears in transverse sections as a small oval collection of similar cells lying between the ependyma and the posterior longitudinal bundle. Each nucleus is a distinct entity, and the two are separated from each other by the approximation and fusion of the lips of the mid-ventral portion of the mesencephalic cavity.

A little later at 35 mm. each main oculomotor nucleus has begun to separate into two distinct parts, a pyriform mass, the ventromedial nucleus, and an oval dorsolateral nucleus. The median nucleus is recognized between the wider ventral portions of the ventro-medial nuclei (fig. 7). This series exhibited a more advanced condition at 35 mm. than Mann's series (1926-27).

By the ninth week of gestation (40-45 mm.) the mesencephalon measures 4 mm. in the antero-posterior diameter and 5 mm. in the transverse. One characteristic feature at this period is the grouping of cells in all the nuclear masses of the tegmentum. The main oculomotor nucleus on each side now exhibits three groups of cells, ventromedial, dorsolateral and accessory. Perlia's median nucleus lies in the mid-ventral line between the three lateral groups. The accessory group is the smallest and is situated on the dorsal aspect of the dorsolateral group. Mann (1926-27) recognized similar groups at 48 mm. Owing to the enlargement of the other nuclear masses in the tegmentum, the oculomotor nuclei and the posterior longitudinal bundles occupy a more dorsal position, and the cavity is becoming reduced to aqueduct dimensions.

In fœtuses of 5·0 cm. length (10 weeks), the oculomotor nucleus is seen to have completed its organization into groups. There are four on each side with Perlia's nucleus between them (fig. 8). The ventromedial and dorsolateral groups of the main nucleus are clearly seen, and the accessory group is separated into two parts, which lie nearer the floor of the aqueduct. The accessory groups occupy the positions of the nuclei of Edinger-Westphal and Darkschewitsch respectively in the adult. Mann (1926-27) identified similar groups in a 75 mm. fœtus. This author states that the Edinger-Westphal portion is better seen in the early stages, since later on the cells stain less intensely and become more widely separated. This is borne out in the present investigation.

The oculomotor cells are by now (5·0 cm.) typical small multipolar neurones, but those of the accessory nucleus are not quite so large as those of the main nucleus. The main processes stream ventrally through or around the red nucleus to their superficial origin in the interpeduncular

space, the basis pedunculi being well formed at this stage. The fibres of the posterior longitudinal bundles appear to be partly disposed among the neurones of the oculomotor nucleus.

Between the eleventh and fourteenth weeks (6·0-9·0 cm.) the four lateral groups and the median group of the oculomotor nucleus are evident, but a complex fibre network, formed by the cell processes and the posterior longitudinal bundle, envelops them. The main axon processes pursue their course ventrally through the fibre meshwork and become bundled together, although it is not possible always to recognize from which group of neurones the fibre bundles issue.

Throughout its development the trochlear nucleus appears in transverse sections as a single semilunar group of neurones, and never seems to be so thoroughly involved in the posterior longitudinal bundle as are the component parts of the oculomotor nucleus. Its cells are similar to those of the main oculomotor nucleus. Pearson (1943) describes a subdivision of the trochlear nuclear column into a larger cephalic and a smaller caudal part in more than 30 per cent. of his specimens. This was not observed in the present series.

By mid-term (14 cm.) the several nuclei of the oculomotor complex are outstanding (fig. 9). Larger and smaller sizes of neurones occur, the former in the median, ventromedial and dorsolateral parts, and the latter in the accessory parts.

According to Keene and Hewer (1932-33) myelination of the trochlear and oculomotor nerve-fibres commences about the fourteenth week (9 cm.), and is heavy by the twenty-sixth week (21 cm.). In the present series confirmation of the commencement of myelination was not obtained, but at 18 cm. (23 weeks) Weigert preparations showed heavy myelination of both nerves.

In the second half of fœtal life the architecture of the oculomotor and trochlear nuclei is unchanged, although, owing to the complexity of the fibre pattern, the different parts are not identified so easily. The neurones increase steadily in size, but are outstripped in this respect by those of the mesencephalic nucleus of trigeminus, and equalled by those of the substantia nigra. By the fifth post-natal year the oculomotor and trochlear neurones have attained their maximum size.

Conclusions.

(1) The somatic efferent column is the first to arise in the mesencephalon. It originates in the mantle layer in the embryo of 10 mm. length.

(2) At the 13 mm. stage the oculomotor fibres emerge from the ventral

surface of the mid-brain. The posterior longitudinal bundle is established in relation to the somatic efferent column at this period.

(3) In the embryo of 16 mm. length the trochlear fibres have reached the alar region where they decussate and emerge dorsally.

(4) A median group of cells derived from the mid-ventral proliferation joins the two lateral oculomotor nuclei at 19 mm. The median group is regarded as Perlia's nucleus.

(5) At the 35 mm. stage each lateral oculomotor nucleus is separated into two parts, ventromedial and dorsolateral.

(6) At 4·0 cm. the accessory group is recognized.

(7) By 5·0 cm. the accessory group is divided into two parts occupying the positions of the nuclei of Edinger-Westphal and Darkschewitsch in the adult.

(8) No grouping in the trochlear nucleus was observed.

The author wishes to express her best thanks to Professor F. Wood Jones and Dr. Una Fielding for their encouragement, advice and criticism; to Mr. H. Gooding for technical help and the photographs; and to Professor Daniel Dougal, Dr. G. Stewart Smith, Dr. Mary Evans and Dr. Walter Calvert for their kind co-operation in collecting the embryos and fœtuses used in these investigations.

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PLATE VIII.

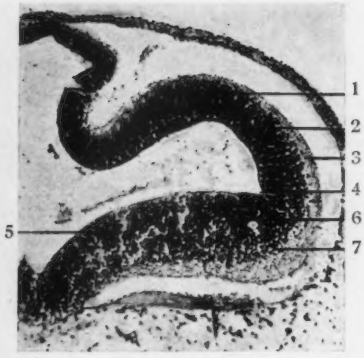

FIG. 1

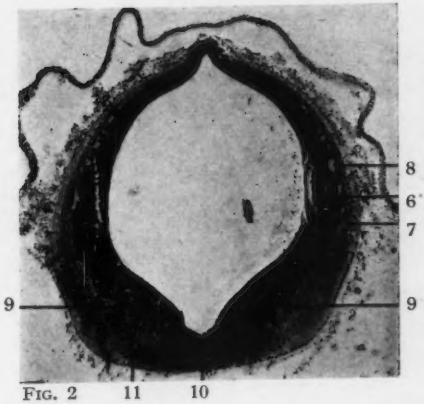

FIG. 2

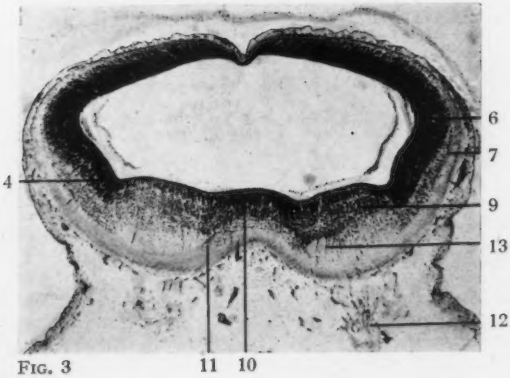

FIG. 3

To illustrate article by E. R. A. Cooper.

PLATE IX.

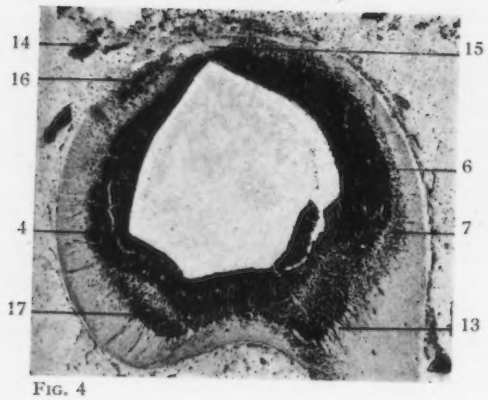

FIG. 4

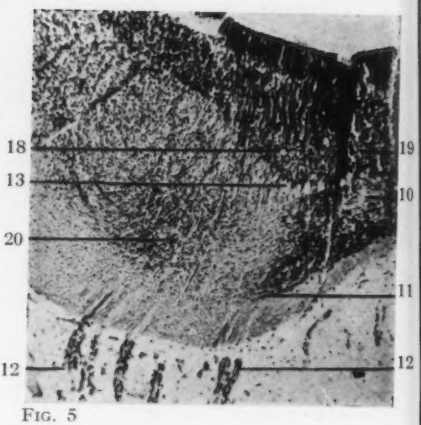

FIG. 5

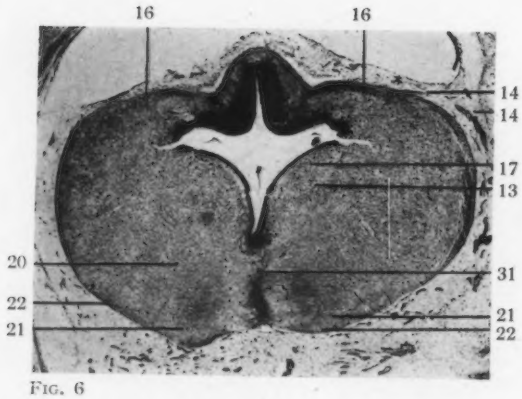

FIG. 6

To illustrate article by E. R. A. Cooper.

PLATE X.

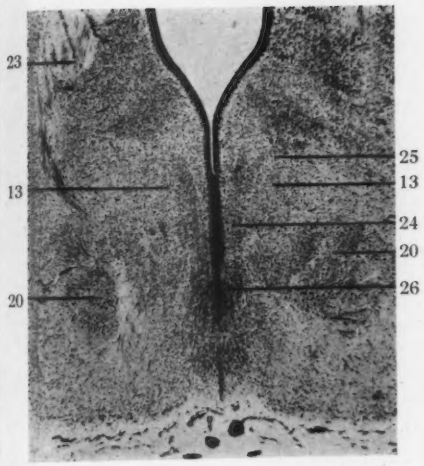

FIG. 7

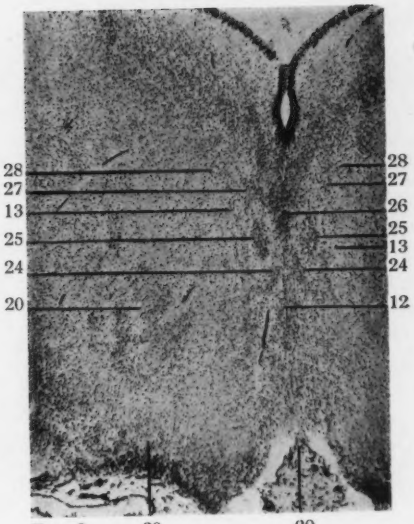

FIG. 8

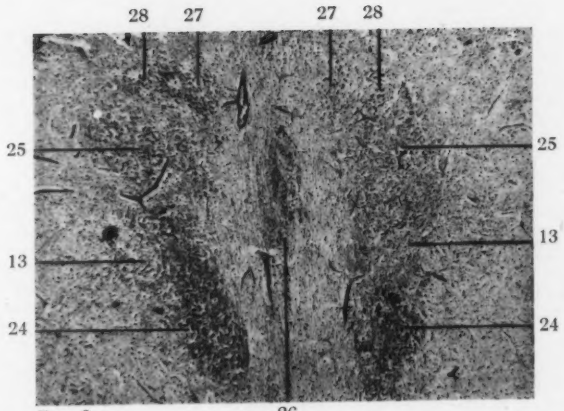

FIG. 9

To illustrate article by E. R. A. Cooper.

PERLIA, (1889), (Von Graefe's) *Arch. f. Ophth.* Bd. **35**, 20. (Quoted in Kappers, Huber and Crosby, 1936.)
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LEGENDS.

FIG. 1.—Mesencephalon. 8·5 mm. embryo. ×80.
FIG. 2.—Mesencephalon. 10 mm. embryo. ×30.
FIG. 3.—Mesencephalon. 13 mm. embryo. ×30.
FIG. 4.—Mesencephalon. 16 mm. embryo. ×45.
FIG. 5.—Basal lamina of mesencephalon. 19 mm. ×75.
FIG. 6.—Mesencephalon. 22 mm. embryo. ×25.
FIG. 7.—Basal region of mesencephalon. 35 mm. ×45.
FIG. 8.—Basal region of mid-brain. 5·0 cm. fœtus. ×30.
FIG. 9.—The oculomotor complex. Mid-term. ×45.

KEY TO ILLUSTRATIONS.

(The use of a hand lens is recommended in examining the photographs.)

1.—Alar lamina.
2.—Mantle layer
3.—Marginal layer.
4.—Interlaminar sulcus.
5.—Basal lamina.
6.—Zone of congestion.
7.—Zone of spread.
8.—Fibres of trochlear nerve.
9.—Somatic efferent column (oculomotor nucleus).
10.—Mid-ventral proliferation.
11.—Lateral angle of (10).
12.—Oculomotor nerve.
13.—Posterior longitudinal bundle.
14.—Trochlear nerve.
15.—Decussation of trochlear nerves.
16.—Alar cells creating the tectum.
17.—Trochlear nucleus.
18.—Lateral part of oculomotor complex.
19.—Median part of oculomotor complex.
20.—Red nucleus.
21.—Substantia nigra.
22.—Descending cerebral fibres (crus).
23.—Fasciculus retroflexus.
24.—Ventro-medial nucleus of oculomotor nucleus.
25.—Dorsolateral nucleus of oculomotor nucleus.
26.—Median nucleus of oculomotor nucleus
27.—Accessory nucleus (1) of oculomotor nucleus.
28.—Accessory nucleus (2) of oculomotor nucleus.
29.—Interpeduncular space.
30.—Basis pedunculi
31.—Decussation of brachia conjunctiva

NEUROLOGY AND PSYCHIATRY.[1]

Their Common Problems.

BY ANDREW PATERSON.

Brain Injuries Unit, Edinburgh.

Both neurology and psychiatry have in the past contributed to our understanding of the causes underlying abnormal human behaviour. The psychiatrist has busied himself particularly, though not exclusively, with what is called the psychogenic origin of such behaviour. The neurologist, recognizing that damage to the brain may give rise to abnormalities of behaviour, has attempted to account for those abnormalities in terms of theories of brain functioning. Though their studies would appear to converge on this most important problem, there has been in this country in the past a tendency for them to pursue separate paths, to be not a little suspicious of each other and to maintain in isolation their own traditional concepts. In the last few years, however, a rapprochement between neurology and psychiatry has been in evidence. In the firm belief that there is no essential opposition between the two studies, this paper attempts to investigate the relationship of the dual systems of ætiology adopted in explaining human behaviour.

Human Behaviour.

In the term human behaviour, I include any and every activity of man with which he can be occupied at any one time. It does not include all activity such as, for example, movements which occur automatically, or as reflexes outside of consciousness. In the mental sphere behaviour would include processes such as imagination, perception and abstract thinking. I include these in the definition of behaviour because the behaviourist school of psychology limit behaviour to any response expressing itself in movement measurable in a laboratory and exclude acts of thinking which, although having no specific movements attached to them, are yet very real human activities.

Down the ages human behaviour and the mechanisms which make it possible have been a constant subject of inquiry and speculation. At

[1] A Paper read to the Society of British Neurological Surgeons, June 4, 1945.

the present time there are two systems of explanation, competing on more or less equal terms in accounting for human behaviour. These are the concepts of physiology on the one hand and of psychology on the other. The sharp distinction between those two systems of interpretation is in some way bound up with the outworn dualism of mind and matter. I shall try to show that the distinction between psychogenic and physiogenic is a practical one, that no fundamental opposition is implied and that they represent different selections from the events which determine the behaviour in question.

The brain provides the immediate conditions on which all human behaviour depends. Damage the brain in any or all of its parts, and there are corresponding changes in the behaviour of the organism; they may be difficult to interpret but they are there. If the brain is damaged enough, behaviour, as we have defined it, ceases to exist.

Many objections are raised to this view on entirely inadequate grounds. It is dubbed materialistic, or as reducing the dignity of human behaviour to mere biochemical change within neurones, or to mechanical interaction between a maze of sensorimotor arcs. This objection arises from the common misconception that an effect is always like its cause. As the philosopher Hume observed, when one billiards ball hits and imparts its motion to another, an effect is produced which is like the cause. This typifies the causal relationship to most people but it entirely neglects the real qualitative differences among objects and among events. The conditions which determine the colour blue appearing are a light vibration of a given wave-length, and all the conditions within the retina and brain which subserve light perception. But, although these are the conditions of blue appearing, blue is a quality quite different from any of them. Similarly, though processes in the brain are conditions of human behaviour in all its forms, even abstract thought, this in no way implies that human behaviour can be reduced to them. The view that the brain provides the immediate conditions of behaviour may be rather crudely summed up in the phrase—the brain is the organ of mind. Such a statement is an over-simplification, as the "mind" cannot justly be compared with the physical functions of other bodily organs. The brain does not secrete thought as the liver secretes bile.

Physiological Theories.

Let us consider one or two of the physiological theories which have claimed to explain the function of the brain and accordingly the produc-

tion of human behaviour. Until recently, the central nervous system, including the brain, was considered as a complicated system of sensorimotor arcs. Hughlings Jackson (1932) wrote:—

"I carry the doctrine of sensorimotor constitution of the central nervous system further than anyone else, so far as I know, since I urge that the highest cerebral centres . . . represent parts of the body as certainly as that of the lumbar enlargement does."

This hypothesis proved invaluable to Jackson in developing a number of theories which have thrown much light on the functioning of the brain. Sherrington showed, by experimental techniques, that the action of the spinal cord isolated from the brain could be explained completely by the integration of a vast number of spinal reflexes, sensorimotor in type. Each reflex could be regarded as acting in a mechanical and automatic way. Sherrington himself believed that the brain would be found to be more than an integration of these sensorimotor reflexes, and in his Gifford Lectures, Man on his Nature (1940), he finds some evidence that the brain originates activity spontaneously, and is not a mere machine, driven by sensory stimuli to produce movement along motor nerves. But notwithstanding the caution of the experts, the view prevails that the behaviour of man can be explained in sensory or motor terms alone. Hence there arises an artificial and misleading tendency to classify all activity into one or other of those categories. An obvious fallacy appears in the case of complicated thought processes, where it is impossible to disentangle sensory from motor components, and the attempt is equally difficult in concrete tasks such as visual constructional activity, where the gnostic component is indissolubly mingled with the praxic one. Clearly new concepts are required for dealing with the products of the integrations which take place at the highest levels of the brain. But, in spite of its shortcomings at those levels, the concept of the sensorimotor reflex has contributed greatly to the advancement of neurological knowledge.

Another physiogenic theory which sets out to account for the complexities of human behaviour is that of Pavlov. He found that an artificial stimulus becomes linked with an inborn response when exhibited before the natural stimulus for that response. He attempted to explain all human behaviour on this pattern and thought that all learning consisted in the setting up of complicated chains of conditioned responses. Both the technique and the conditioned reflex thereby produced are essentially physiological, in fact behaviouristic in the narrow sense which I have explained above. The findings were obtained in quite artificial settings, in animals dominated at the time by one strong urge, and physically

restrained so that they could give no other response than the one desired by the experimenter. Some aspects of human behaviour can reasonably be interpreted in terms of the conditioned reflex. There are others, however, especially those of the higher cognitive order, such as insight into a problem and certain facts of human learning and motivation, which Pavlov's principle entirely fails to explain, or explains only by postulating elaborate systems of inhibition and disinhibition which, like other speculative ventures, are capable neither of proof nor disproof.

Although, as we have said, Pavlov's technique and conditioned reflex were physiological, and although the cerebrum required to be intact for the establishing of conditioned reflexes, the latter have not contributed in any major way to the understanding of cerebral mechanisms. Pavlov was obliged to postulate a "trace" theory, in order to bring the conditioned stimulus into touch with the unconditioned reflex. The word "trace" has been generally adopted, in psychology at least, for that modification of the brain substance which past experience must be postulated to leave behind in order that learning and recall be made possible. Neural disposition and engram are synonyms. Before brain anatomy was at all well known, traces left by experience (visual experience was taken as the archetype) were regarded as lasting impressions similar to impressions on a photographic plate. When more became known about the brain structure, traces became some kind of modification between nerve-cells, and many theories regarding these have been put forward—growth of new processes, increase in conducting substance, lowering of threshold, &c. Recently Köhler has suggested that traces should be regarded as having the properties of electric fields. The multiplicity of these theories is a sure indication of our ignorance regarding the nature of the modification in the brain left by earlier experiences.

Electro-encephalography.

Passing now from mere theories to the actual work which is being done in the direct investigation of the brain function, we find that a new approach to its study has been made in the past two decades through the physical technique for measuring very small electrical changes in nerve cells. This has resulted in the present development of electro-encephalography, where the electrical changes on the brain surface can be read off from electrodes placed on the scalp. By the wisdom, caution and modesty of those who first investigated those changes, no extravagant theory of brain function and no explanation of mental processes on that basis have

been put forward. The present technique has its limitations in that the recordings are from the brain surface only, and through the skull. But after explaining the shortcomings of the present methods in electro-encephalography, Professor Adrian (1945) says:—

"Such a technique may soon be superseded; judged by the standards of modern physics, it is already obsolete, and I think we should look forward to the possibility of being able to record all the electrical events within the brain in far greater detail and without hindrance from the skull." Such an electrical survey, he continues, "could scarcely avoid giving some entirely novel information about what is happening in the brain when we think or solve problems or decide what to do."

But, lest what he says may arouse undue optimism regarding the solution of our philosophical problems, Adrian adds: "I have an uneasy feeling that we shall find a catch somewhere."

Psychological Theories.

We now come to the psychogenic explanation of human behaviour, a popular and important one. The principal fact lying behind it is that any organism, and this applies particularly to the human, is determined by its past—the past lives in the present, past experience of the organism determines what it is now, and what kind of behaviour it will display in any situation. We can safely say, then, that an organism is, in large part at least, a function (in the mathematical sense) of its past. It is only reasonable that we should regard experiences in the past as conditions of behaviour shown in the present. These past experiences are justifiably called psychogenic causes, and provide the content of psychogenic ætiology. Such ætiology represents the historical explanation of behaviour and has all the shortcomings which history in any other form presents. It is selective and dependent upon the interests of the investigator and upon the ability of the individual accurately to recall his past.

There is another aspect of psychogenic ætiology to which I must make reference. It explains human behaviour in terms of present instincts, desires, urges and emotional tendencies, and does not, at first sight at least, appear to have any historical reference. Such concepts are solidly embedded in our language, and constantly applied in everyday speech to account for human actions. They introduce the idea of a psyche, a vital dynamic principle which initiates all human behaviour; it is the elan vital of Bergson, the entelechy of certain schools of biologists, the libido of Freud.

Freud, faced with the barrenness of contemporary neurology and physiology in accounting for man's emotional and instinctive behaviour, canalized and developed the popular explanation of behaviour in terms of vital principles. He concluded that the vital principle or urge was essentially the sex urge, and called it the libido. Adult behaviour resulted from the differentiation of the libido in various directions, from fixations at certain immature stages, and from frustration due to the organism's clash with its environment. Much of the abnormal behaviour exhibited by the adult, Freud explained as a regression to earlier modes of reaction and stages of fixation. Present urges and drives have little or no content apart from what they derive from the study of their development and their vicissitudes in the history of the individual. On introspection these conative processes are lost in the vague undifferentiated appreciation of body feeling. They are not facts presented in immediate experience but concepts or hypotheses elaborated to account in retrospect for our own behaviour, or by reflection for the behaviour of others. Freud has given content to these concepts, and the whole process of psycho-analysis is aimed at elucidating their history. So again we return to the view that psychogenesis is essentially an explanation of present behaviour in terms of past experience.

Psychogenesis *versus* Physiogenesis.

Behaviour which arises on a psychogenic basis is often contrasted with that occurring on an organic one. This problem arose acutely at the beginning of this war in connection with behaviour changes following head injuries. A decision, it was thought, had to be made as to whether abnormal emotional reaction and behaviour were due to a man's previous constitutional response to a difficult situation, or whether the damage to his brain had caused him to react differently from his normal behaviour. Lewis (1942) gives a comprehensive analysis of this problem.

Much confusion arises from regarding psychogenic as being different from physiogenic or organic behaviour. If what I have said above is correct, any experience, whether it be normal, neurotic, or arising from known brain damage, has a basis both in the functioning of the brain, i.e. physiogenic, and in the previous experience of the individual, i.e. psychogenic. So far the physiogenic conditions are little known although cerebral physiology would appear to be making some progress towards their elucidation. The psychogenic conditions, that is, the relevant history of the individual, can be known to a considerable extent, through recall of the past by the individual and the testimony of others. In the absence

of any gross cerebral lesion, the part played by the brain in producing behaviour is ignored and the past history of the individual and his personality pattern, which are known, become in the eyes of some investigators the dominant ætiological factor. When abnormal behaviour occurs in the presence of a known brain lesion, it is clear that the brain has played an important part in producing such behaviour. The latter is accordingly termed physiogenic or organic. Hence psychogenic becomes associated with the behaviour reaction of the intact brain, and organic with the damaged brain.

The above opposition of physiogenic and psychogenic implies, however, that the brain has no part to play in that behaviour which is determined by the previous history of the individual, and, conversely, that the previous history plays no part in determining the behaviour arising from brain damage. Both views are equally fallacious. The term constitutional may suitably be used to describe behaviour where the brain is intact, and post-traumatic should indicate that component of behaviour which results from brain damage.

It is often forgotten that Freud (1922) recognized that his psychoanalytic doctrine " in reality but a superstructure . . . will have to be set on its organic foundation at some time or other." This correlation with physiological processes has not so far been possible, because of our ignorance of what these processes are, or even where they are located in the brain. In the absence of such correlation, the psychogenic theory was elaborated in isolation from other considerations, and unfortunately became, in the eyes of some of its adherents, entirely self-sufficient. A change of attitude has become apparent, perhaps in view of the new physical methods of treating psychoses, and a new interest is being taken in the relationship of psychogenesis and physiogenesis.

Perception.

I should like to bring out the difference in our knowledge of the physiological conditions underlying two different aspects of human behaviour—the perceptual side and the emotional-instinctive side. This divergence accounts for the different way in which these two highly developed activities of man have been treated in the past. The approach to one has been by way of neurology, to the other by way of psychiatry. Let us take vision as representing perception in other fields. Visual perception has for long been associated with a physiogenic explanation, or, in clinical terms, with neurological conditions. The observa-

tions on which this is based are as follows: Visual perception taken as a fact is more or less uniform from one person to another and does not depend for its maturation or development on any specific circumstance or environment which might vary from one individual to another. The history of its development can therefore be neglected in studying the process itself. Again, each mode of perception enjoys a relative independence from the rest of the individual's experience and has a definite part of the cerebrum set aside for the physiological integrations which render it possible. Interference with hearing does not in any noticeable way interfere with vision. Each perceptual field is subserved by a primary pathway which is morphologically distinguishable and conducts the sensory stimuli to the higher centres.

In the case of vision, not only is the primary visual pathway known, but knowledge is gradually being built up by neurologists of the approximate localization in the occipital or occipito-parietal lobes of some of the integrations rendering possible the various processes responsible for normal visual perception. For example, interference with the visual recognition of objects is associated with localized lesions in the dominant parieto-occipital area. Holmes, on clinical grounds, has established the point-to-point correlation between the retina and its projection on the striate areas of the occipital cortex. Bilateral lesions in the region of the angular gyrus may give rise to visual spatial disorientation in central vision. Recently Symonds (1945) has shown that visual orientation in depth can be selectively impaired by a small lesion in the right occipital lobe. These and other observations indicate that visual perception is built up in elaborate fashion in the occipito-parietal areas and that there is considerable uniformity from one brain to another in respect of the areas subserving the various components of vision.

The chances of working out further the processes of integration underlying visual perception appear to be good. The accurate localization of lesions not so far possible may be achieved if an electrical survey of the whole brain can be made in the future. So far, the functions of small areas of the brain cannot be selectively and temporarily interrupted in the ordinary waking state without permanent damage to the neural structure. Is it too much to hope that this may become possible in the future, when the electrical activity of the brain is better understood? Some encouragement in this belief may be gathered from consideration of electrical shock therapy. A strong current passed through the posterior frontal region of the brain can produce in some way an interference with the mechanisms

underlying emotional reactions. Köhler and Wallach (1944) reported an experiment whereby they tried, by passing a strong electric current through one occipital lobe, to interfere selectively with the physiological mechanisms within that lobe. Temporary changes in the opposite half of the visual field were observed. (The writers, however, advise that this experiment should not be repeated, for the subject suffered during the subsequent fortnight from severe headache and persistent mental depression.) These methods are as yet essentially crude, but give indications of what may be possible in the future with more refined techniques and a better understanding of how an electric current affects nerve functions.

One further characteristic of visual perception makes its study more easy than that of emotional reactions. Lesions of the parts of the brain subserving visual perception in general give rise to a deficit in function—some part of the visual function is missing—it may be, for example, depth perception. Hallucination is, of course, the obvious exception but the general rule is a deficit. This can usually be measured by experimental technique and most often with the collaboration of the patient who recognizes the deficit.

Emotion and its Cerebral Mechanisms.

When we pass on to consider the emotional and instinctive aspect of human behaviour, the contrast is very obvious. We saw that the visual process could be considered in isolation from the rest of experience and is uniform from person to person independent of the general situation. But our mood at any one moment cannot be considered in similar isolation. If it is raining, my visual process will remain very much the same as ever it was, but my general mood reaction to the task in hand may be much influenced by the weather.

Again, there is no accurate way of differentiating one emotional reaction from another. Introspection at the time merely changes or disperses emotion, giving little indication as to what it was. The language of the novelist, in which we usually describe emotional reactions and mood changes, is an extremely inaccurate instrument for this purpose. Besides this difficulty in psychological discrimination of mood states and motivations at any one moment, the parts of the brain which subserve this kind of reaction are very far from being known. Abnormal emotional reactions appear in association with lesions from an extensive area in the cerebrum and mid-brain, particularly in the frontal lobes, the corpus striatum, thalamus and hypothalamus. Again the anxiety or catastrophic reaction which accompanies the performance of an impaired skill, such as occurs

in cases of aphasia due to cortical lesions, may not inconceivably have some focal cortical significance. The view would find some support in the discovery in recent[1] years that the autonomic nervous system is widely represented in the cerebral cortex (Fulton, 1944).

The study of emotional behaviour in man is further complicated by the fact that for practical purposes and also on the basis of certain clinical observations the emotional experience must be divided into an affective component, the characteristic feeling of emotion, and its motor expression. The pattern of the motor expression is detailed and specific for each of the basic emotional reactions, but not for their finer differentiations, such as interests and sentiments. The researches of Bard (1934) and others on animals have shown that the hypothalamus is a main motor nucleus subserving the expression of at least the basic emotions of rage and fear. Clinical observations tend to confirm the same role for the hypothalamus in man.

The function of the cerebrum in connection with the motor expression of emotion was till recently regarded as being mainly inhibitory. Changes in emotional behaviour following cerebral damage were interpreted as release phenomena occurring in the hypothalamus and lower centres. Now, however, that both sympathetic and parasympathetic reactions are known to be represented in the cerebral cortex, it may reasonably be assumed that the cortex makes a positive and immediate contribution to the pattern of the autonomic component in emotional behaviour. This contribution would be in the direction of greater variety and complexity of response with a finer adjustment to the situation calling it forth. Such a view would be more in keeping with the function of the cortex formulated by Hughlings Jackson, namely inhibition of the lower centres but also as adding refinement and discrimination of response both in the motor somatic and sensory fields.

As to the structures subserving the affective side of emotion, there is as yet no conclusive evidence. The view set forth by Head and Holmes that the thalamus is the seat of the pleasant and unpleasant feelings associated with certain sensory abnormalities has had its critics. The criticism is well summarized by Lashley (1938). This investigator also points out that the extension of the theory of Head and Holmes in regard to

[1] But Dr. George Riddoch has kindly drawn my attention to an article by Leonard Guthrie (1918). At that time it was recognized that trophic and nutritional changes in a limb might follow a lesion of the corresponding parietal lobe. Such changes clearly arose from impairment of the autonomic nervous system represented in that lobe.

dysæsthesia to make the thalamus the seat of all affective experiences is unjustified.

The cerebrum appears to contribute the dynamic motivational component of emotional experience. In the thalamic and hypothalamic preparations in animals the rage response does not as a rule outlast the stimulus. But the effects, in an intact animal, of a fight with a neighbour may be observed over a few hours. The maintenance of relatively constant emotional attitudes in man, such as interests, political orientations, &c., can be observed over periods of years.

These observations indicate how complex are the brain mechanisms subserving emotional behaviour in man, and how little is known about them. Again, when we consider the individuality of the emotional and temperamental pattern in any one person, it is safe to assume that there is a corresponding individuality in the pattern of brain mechanisms subserving it. This complexity and individuality is in striking contrast to the relative uniformity and consistency of visual and other perceptual fields.

Co-operation in Neuropsychiatry.

In face of the fickleness of emotional reactions and personality traits compared with the relative uniformity and consistency of the perceptual process, it is small wonder that the clinical neurologist has devoted little time to the study of the former. A short chapter on the common affective disturbances or neuroses is usually tucked away at the end of his textbook of neurology. The psychiatrist, on the other hand, has made some sense of the problems presented by human behaviour in the emotional sphere. With the help of his own concepts, and the technique of the historical method, he has succeeded in elucidating a few of the antecedents or conditions of abnormal human behaviour. He can then use psychotherapy in alleviating the symptoms of the neuroses or minor maladjustments from which his patient may suffer. Rightly regarded, psychotherapy is a process of re-education in the sphere of emotional and social adjustments. This process of re-education is of no avail, however, in the major abnormalities of behaviour, and empirical methods have been discovered which modify them favourably. They clearly take effect on the nervous mechanisms subserving emotional experience. Electric shock therapy I have already mentioned, and another method is prefrontal leucotomy. These procedures can claim and are justified by some outstanding successes, but there are many cases in which the more or less uniform technique fails to produce uniform results. These inconsistencies

might be expected on contemplating the crudeness of the destructive methods and the probability that the physiological mechanisms interrupted, are integrated in an individual pattern corresponding to the individuality of the patient.

It is the individuality of each of these cases that demands the closest co-operation between the neurologist and the psychiatrist. Any personality change, whether arising from therapeutic interference with function, a tumour, localized contusion, or associated with spontaneous epileptic disturbances, should be assessed against the previous behaviour pattern. It is only by such collaboration that full advantage can be taken of the advances in technique that physiology may provide, thereby furthering our knowledge of the psychological and physiological determinants of human behaviour. It is this collaboration which appears to justify the application of the term neuropsychiatry to their combined studies and investigations.

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Notices of Recent Publications.

Introduction to Clinical Neurology. By Gordon Holmes. E. and S. Livingstone, Edinburgh. 1946. Pp. 179. Price 12s. 6d.

To the many who, during the past thirty years, have come from all corners of the globe to learn neurology at Queen Square, the teaching of Dr. Gordon Holmes at the bedside and in the lecture theatre will be amongst their most vivid and happy recollections. To few teachers of clinical medicine in our day has it been given to command the affection and respect of so numerous and so distinguished a body of post-graduate students. Hence, all who have had the good fortune to learn their clinical neurology from Dr. Holmes will welcome the memories which this "Introduction" will awaken, while a younger generation will find in it the quintessence of the experience of a master of clinical neurology and of its teaching.

Neurology is perhaps the most lucid and logical branch of medicine, and this it owes largely to those foundations of anatomical and physiological knowledge upon which it necessarily rests. The content of this knowledge and its mode of application to clinical examination and diagnosis are concisely and clearly exposed in these pages. The methods of clinical examination of motor and sensory systems and of the reflexes, and the forms of disorder of these systems, are all fully dealt with, while the visual system, the speech function, the postural and vestibular functions, the bladder and rectum and the autonomic system all have their chapters. The book is well illustrated by a number of original diagrams. Within a small compass the author has presented a summary of relevant knowledge that every post graduate student of neurology will need, and every professed neurologist delight to read.

An Atlas of the Basal Ganglia, Brain-stem and Spinal Cord. By H. A. Riley. The Williams and Wilkins Co., Baltimore. 1943. Pp. 708. 264 Plates with a list of structures and references. Price £3 15s.

This fine atlas is based on Weigert-Pal sections through the brain and spinal cord chiefly in the horizontal and coronal planes, but a few in the sagittal plane are also included. The sections are selected from a number of normal brains and give excellent pictures of the normal structures and these are indicated by initial letters which are amplified on the opposite page. There is thus little difficulty in identifying any of the tracts or nuclear areas illustrated. At most levels two different magnifications are illustrated so that the smaller structures can readily be picked out.

The author devotes 171 pages at the end of the atlas to a "list of structures" in which the main origin and destination of tracts and bundles and the composition of nuclei are shortly outlined. Six pages are filled with references, chiefly to textbooks and monographs.

Along with many excellencies the atlas suffers from certain defects. One is that the lettering on the plates is entirely in capitals and these are so spaced and arranged that it is not always easy to see which letters make up a group.

The list of structures is arranged according to the initial letters of their Latin names which means that N. hypothalamicus dorso-medialis is sandwiched between two parts of the N. habenularis, and the Tractus pontocerebellaris between T. pallido-nigralis and T. pallido-olivaris, an arrangement which makes it difficult to find the reference to a structure and to the plates in which it appears. In certain respects also this list is inconsistent, for example no reference is made to the centro-median nucleus in the description of the thalamus, although it appears elsewhere in the list. References also appear in the descriptions to structures which are not listed, such as the Amiculum and to other structures by names which are not indexed. For example Forel's fields H1 and H2 are referred to as such in the text but are only indexed as Area tegmentalis. All this makes it difficult for any but the expert to use the atlas without constant reference to another textbook of anatomy.

It is a definite blemish on so comprehensive a work that several important segments of the spinal cord, for example C.VI, C.VIII and S.II are not illustrated and it is surely unnecessary that the enlargements of the segments of the spinal cord should vary from × 14 to × 40.

The atlas will prove of great value to the research worker once he has mastered its arrangement and has gained a certain familiarity with its contents, and the author deserves our gratitude for the patient labour which has gone to its compilation.

Experimental Catatonia. By H. H. DE JONG. Ballière, Tindall and Cox, London. 1945. Pp. 225. Price £1 2s.

The author first produced the condition he names "experimental catatonia" by the use of bulbocapnine in animals. In the present work he amplifies these original observations by describing the production of catatonia by a wide range of substances. In all circumstances, he concludes that the underlying pathological process is a cellular asphyxiation of the nervous system, and that in all cases, also, some alteration of liver or of intestinal function is an essential condition of its production.

Very numerous experimental protocols are given, and the impression may be derived from some of them that the conception of catatonia has been so widened to include the phenomena observed that it has lost the necessary quality of scientific precision. There is no index.